

2022 EPILEPSY

ILAE BRITISH BRANCH
18TH SPR TEACHING WEEKEND
14-15 MAY 2022

FROM BENCH TO BEDSIDE
A PRACTICAL GUIDE TO EPILEPSY

EDITED BY F.J. RUGG-GUNN AND H.B. STAPLEY

 **ILAE**
BRITISH BRANCH

STEP TOWARDS SEIZURE FREEDOM*^{1,2}

56% of patients achieved a $\geq 50\%$ reduction in seizure frequency with ONTOZRY[®] 200 mg/day vs 25% of patients with placebo when added to SOC[†] over 12 weeks of fixed dose, double-blind treatment^{†1,2}

21% of patients achieved seizure freedom (100% reduction in seizure frequency) with ONTOZRY[®] 400 mg/day vs 1% of patients with placebo when added to SOC^{†§1,2}

Once-daily oral dosing titrated gradually to the recommended target dose of ONTOZRY[®] 200 mg/day^{¶1}

ONTOZRY[®] is generally well tolerated, with a dose-dependent treatment-emergent adverse event profile.[¶] The most common adverse reactions are of mild-to-moderate severity: Somnolence, Coordination and Gait abnormalities, and Headache^{¶1,3}

*Seizure freedom was a secondary endpoint of the C017 Phase IIb study. The primary endpoints were the $\geq 50\%$ responder rate and % change in seizure frequency.²

ONTOZRY[®] is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.[¶]

[†]In the randomly assigned population at baseline, median number of previous anti-seizure medications (ASMs) taken at any time before the start of the study was 3 (range 2-4); these might or might not have been ongoing during the study. 74% of patients (n=322/437) were taking 2-3 concomitant ASMs during the study.²

[‡]Responder rates for seizure frequency reductions of $\geq 50\%$ from baseline during the maintenance phase were 25% (n=26/102) for the placebo group compared with 56% (n=55/98; OR 3.74 [95% CI 2.06-6.80]; p<0.0001) for the ONTOZRY[®] 200 mg dose group.²

[§]Responder rates for seizure frequency reductions of 100% from baseline during the 12-week maintenance phase were 1% (n=1/102) for the placebo group, 4% (n=4/102) for the ONTOZRY[®] 100 mg group, 11% (n=11/98; p=0.0022) for the ONTOZRY[®] 200 mg group and 21% (n=20/95; p<0.0001) for the ONTOZRY[®] 400 mg group.²

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[¶]Grouped terms: Somnolence: somnolence, fatigue, sedation and hypersomnia; Coordination and gait abnormalities: dizziness, vertigo, balance disorder, ataxia, gait disturbance and abnormal coordination.[¶]

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References: 1. ONTOZRY[®] Summary of Product Characteristics; 2. Krauss GL, et al. Lancet Neurol 2020;19(1):38-48; 3. Sperling MR, et al. Epilepsia 2020;61:1099-108.

ASM = anti-seizure medication; CI = confidence interval; OR = odds ratio; SOC = standard of care.

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International League Against Epilepsy

EPILEPSY 2022

A Practical Guide to Epilepsy

Lecture Notes

Eighteenth Epilepsy Teaching Weekend
14-15 May 2022

University of Birmingham Teaching and Learning Building



Edited by F.J. Rugg-Gunn and H.B. Stapley

LECTURE NOTES for the Eighteenth Epilepsy Teaching Weekend 14-15 May 2022

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Preface

Welcome to the eighteenth Teaching Weekend on Epilepsy for specialist registrars in paediatric and adult neurology, learning disability, neurosurgery, rehabilitation and geriatrics.

We organise this course on behalf of the British Branch of the International League Against Epilepsy and are grateful to UCB Pharma, Zogenix, Angelini, Desitin Pharma, LivaNova and UNEEG Medical for their generous support, without which this would not be possible. We are also very grateful to our many colleagues who willingly give up their time to teach on this course, with no financial reward.

We hope that you find the weekend useful, stimulating and enjoyable, and an opportunity to catch up with old friends, as well as to make some new ones. Many of the Faculty are attending for the whole weekend, so please feel free to approach them at any time.

The Lecture Notes also include material for which there was not time to have a formal presentation this time. We hope you find these Notes useful in the future. The Notes are also to be found on the website www.epilepsysociety.org.uk, along with a range of other useful material for healthcare professional, patients, carers and the wider public.

Fergus Rugg-Gunn

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Introduction

This is the eighteenth Edition of these Lecture Notes. They were first published in 1987 as a summary of the material used in the biannual epilepsy teaching weekend organised under the auspices of the British Branch of the International League Against Epilepsy. Over the years the notes have evolved from a summary into a comprehensive text; for this we would like to acknowledge the hard work of the contributors and previous editors, particularly John Duncan and Ley Sander to whom we are much indebted.

The material contained within this book continues to complement the Epilepsy Teaching Course, and as such takes a broad view of epilepsy. We hope that the contents will be used for teaching on other courses. The chapters can be freely copied for such purposes, as we have deliberately not copyrighted them. We have expanded some chapters and introduced new chapters in response to comments received concerning previous Lecture Notes.

The evolution of this book through the teaching course has meant that it maintains a pragmatic tone, yet covers many topics in detail. For this, we are very grateful to contributors for their accomplished chapters, and to Hannah Stapley for her dedication and tenacity in compiling this edition.

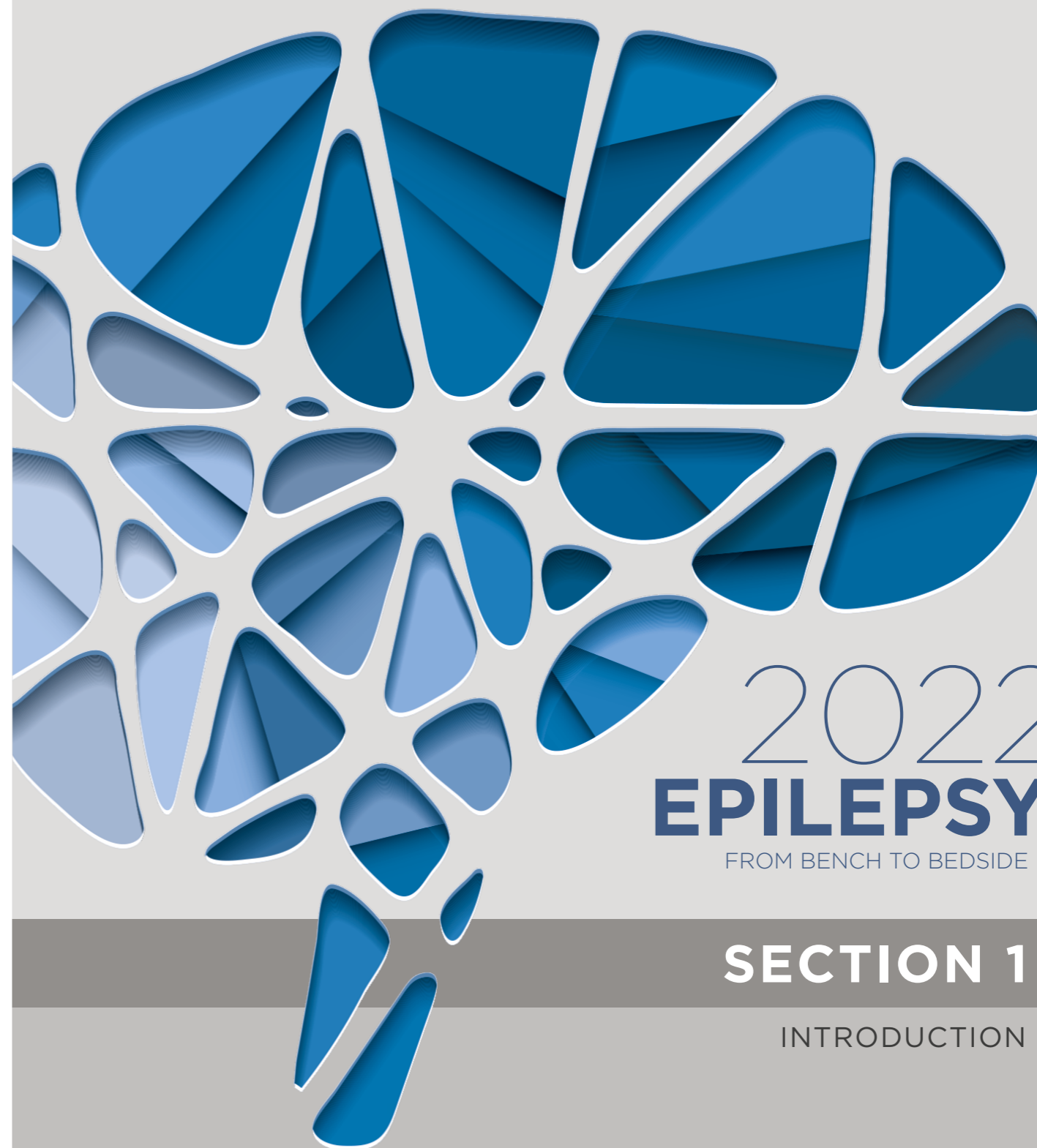
Lastly we would like to thank the sponsors UCB Pharma, Zogenix, Angelini, Desitin Pharma, LivaNova and UNEEG Medical who have given without demands, and the British Branch of the International League Against Epilepsy for their continued support.

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 1

INTRODUCTION

CHAPTER 1

The incidence and prevalence of epilepsy

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The incidence and prevalence of epilepsy

Epilepsy is the commonest neurological condition affecting people of all ages, race and social class. There are an estimated 50 million people with epilepsy in the world, of whom up to 75% live in resource-poor countries with little or no access to medical services or treatment^{1,2}.

Up to the 1960s, early epidemiological studies in epilepsy were carried out in tertiary referral centres which favoured the belief that epilepsy was a chronic, progressive incurable condition with little chance of remission. This is famously expressed by Gowers writing in 1881 that 'The spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case'³.

Since then many epidemiological studies have been published from both developed and resource-poor countries but methodological differences, lack of standardised classification, problems with case ascertainment and diagnostic accuracy have resulted in disparity in study findings, as well as reflecting the heterogeneous nature of a diagnosis of epilepsy⁴.

Diagnostic accuracy is a particular problem in epilepsy as seizures are a symptom of diverse underlying cerebral aetiologies and normally do not have any physical manifestations⁴. Consequently, a definitive diagnosis of epilepsy is often only made after an extended period of follow up, as evidenced in the Rochester study⁵ and the National General Practice Study of Epilepsy (NGPSE), a community-based study of epilepsy in the United Kingdom⁶. Moreover, it has been found that 20–30% of those attending tertiary referral centres with refractory epilepsy do not in fact have epilepsy⁷, with the most common differential diagnoses being dissociative seizures and syncope. As expected, neurologists are better at the diagnosis of epilepsy than non-specialists (mistake rate 5.6% vs 18.9%)⁸, but a misdiagnosis rate of 5% should be considered as the absolute minimum.

Many people with epilepsy may not come to medical attention, either through ignorance or lack of awareness of the symptoms. This is particularly true of absence and minor complex partial seizures, which may only be recognised in retrospect following presentation with a generalised seizure⁹. Indeed in one study of general practices only 20% of patients with seizures suspected the diagnosis prior to medical consultation¹⁰.

Incidence studies

While many people presenting with seizures do so with a prior history of events, between one-third and half present with a single unprovoked seizure^{6,11}. Most studies combine the incidence rates for all newly diagnosed unprovoked seizures (single seizures and newly diagnosed epilepsy) but would be expected to be higher than the incidence of epilepsy in a population followed over a long period of time, as not all people with a single seizure go on to develop epilepsy (defined

as at least two recurrent seizures). This was demonstrated in the Rochester study which followed a population over a 50-year period. The incidence of a first unprovoked seizure was 61 per 100,000 compared to the incidence of epilepsy of 44 per 100,000¹². Overall, while difficult to confirm, the incidence of first single unprovoked seizures is likely to lie somewhere in the range of 50 and 70 per 100,000 in industrialised countries but may be much higher in developing countries¹³.

In general, the incidence of epilepsy in developed countries is taken to be around 50 per 100,000 (range 40–70 per 100,000/year)¹⁴ while the incidence of epilepsy in resource-poor countries is generally higher in the range of 100–190 per 100,000/year¹⁵. While many factors may be contributing to this disparity, it has been shown that people from a socio-economically deprived background are at higher risk of developing epilepsy¹⁶.

In a systematic review of incidence studies carried out, 40 studies were identified, nine of which were prospective, and seven studies identified were from resource-poor countries. The median incidence rate of epilepsy and unprovoked seizures was 47.4 and 56 per 100,000. When the analysis was limited to studies of the highest quality, the median incidence rates for epilepsy and unprovoked seizures decreased to 45 and 50.8 per 100,000¹⁷. In a systematic review of European epidemiological studies, annual incidence rates in studies of all ages ranged from 43–47 per 100,000 person years¹⁸.

A more recent systematic review and meta-analysis identified 33 cohort studies with the median incidence of epilepsy being 50.4 per 100,000 person years (interquartile range (IQR) 33.6, 75.6). The median incidence was lower in high income countries (45.0; IQR 30.3, 66.7) compared to that in low- and middle-income countries (81.7; IQR 28.0, 233.5)¹⁹.

The incidence of epilepsy in Italy in 2011, using a nationwide database (the Health Search CSD Longitudinal Patient Database), was 33.5 per 100,000 person years with a higher incidence in women (women 35.3, men 31.5) and the incidence being highest in people aged <25 years and ≥75 years. This represents one of the lowest incidence rates reported in a European population²⁰.

While there are only few incidence studies from low- and middle-income countries, two recent studies from rural Kenya²¹ and Benin²² provide important data on the incidence of epilepsy in sub-Saharan Africa. In rural Kenya, in a cohort of 151,408 people, 194 developed (convulsive) epilepsy over five years giving a minimum crude incidence rate of 37.6/100,000 person years (95% CI 32.7, 43.3) and adjusted for loss of follow-up an incidence of 77.0/100,000 person years (95% CI 67.7, 87.4). Incidence was highest in children aged 6–12 years (96.1/100,000 person years; 95% CI 78.4, 117.9)²¹. In the study from Benin²², 11,688 people were surveyed and 148 people with epilepsy were identified over an 18-month period, with the prevalence estimated to be as high as 38.4 per 1000 (95% CI 34.9, 41.9). The mean annual incidence was 69.4 per 100,000 person years with an estimated cumulative incidence of 104.2 per 100,000 person years.

Prevalence studies

Studies have shown prevalence rates for active epilepsy in developed countries of between 4 and 10 per 1000¹⁵, although most studies give a prevalence rate of active epilepsy of 4–7 per 1000. In a systematic review¹⁸ it was found that the range for prevalence rates in Europe was 3.3–7.8 per 1000 with a median prevalence rate of active epilepsy of 5.2 per 1000. Studies with the lowest prevalence rates reported were from Italy; 3.3 per 1000 in Sicily²³ and 3.01 per 1000 in the Aeolian Islands²⁴, although the authors of both studies suggest that prejudice towards people with epilepsy and the low prevalence rates may result from patients' desire to conceal the diagnosis to avoid perceived social disadvantages. In the Rochester study the prevalence of active epilepsy, calculated at 10-year intervals over 50 years, ranged from 2.7 per 1000 in 1940 to 6.8 per 1000 in 1980²⁵.

More recent studies using patient reports from Norway (crude prevalence rate 11.7 per 1000; active epilepsy 6.7 per 1000)²⁶ and Ireland (life prevalence 10 per 1000; treated epilepsy 8.3–9.0 per 1000)²³ suggest higher prevalence rates in western countries. The median lifetime prevalence in developed countries has been estimated to be 5.8 per 1000 (range 2.7–12.4) with a median prevalence of active epilepsy of 4.9 per 1000 (range 2.3–10.3)². In the Italian study the crude prevalence of epilepsy in 2011 was 7.9 per 1000 (men 8.1, women 7.7) with the prevalence being highest in those aged <25 years and ≥75 years²⁰.

The lifetime prevalence of seizures (the risk of having a non-febrile epileptic seizure at some point in an average lifetime) is between 2 and 5%. The difference between the lifetime prevalence and prevalence of active epilepsy implies that for the majority either the condition remits or the patient dies.

Evidence from community-based studies have shown that 70–80% of people with epilepsy will achieve remission, usually in the early course of the condition, and indeed the longer epilepsy remains active the poorer the prognosis²⁸. (Prognosis is reviewed in Chapter 36.)

Factors influencing incidence and prevalence

Most incidence studies show that epilepsy is more common in males than females, both in developed and resource-poor countries but this difference is rarely significant²⁹.

In the systematic review of incidence studies, the median annual incidence of epilepsy was 50.7 per 100,000 for males and 46.2 per 100,000 for females¹⁷. Incidence rates also vary considerably with age. Studies in the industrialised world consistently show a bimodal distribution. There is a very high incidence in the first year of life and in early childhood, with a relative decrease in adolescence. Incidence is at its lowest between the ages of 20 and 40 and steadily increases after age 50, with the greatest increase seen in those over age 80. There is evidence that the incidence of epilepsy is now higher in elderly people than children³⁰.

The temporal changes in incidence of epilepsy in Finland between 1986 and 2002 were examined using a nationwide database. The total incidence decreased significantly from 71.6 to 52.9 per 100,000 per year during that time. The incidence decreased in children and adults but increased in the elderly, particularly in women³¹.

Incidence and prevalence rates of epilepsy tend to be higher in resource-poor countries. The highest reported rates of epilepsy have been found in South America; in a well designed study in Ecuador the incidence rate was 122 per 100,000/year³².

The prevalence of epilepsy appears to be lower in Africa, while studies from Asia (mainly China and India) have demonstrated rates similar to those in the Western world. Moreover there can be marked variation in incidence and prevalence rates between different regions within the same country, although most but not all studies have shown that rates are higher in rural than in urban areas¹⁵. No consistent racial differences in epilepsy have been found and in a study of incidence in a low-income community in New York, the incidence among Hispanics (36.5 per 100,000) was similar to that of non-Hispanic whites (39.4 per 100,000) and non-Hispanic blacks (37.6 per 100,000). Lower income was, however, associated with a higher incidence of epilepsy in all ethnic groups³³.

The median prevalence of lifetime epilepsy in developing countries has been estimated to be 15.4 per 1000 (range 4.8–49.6) in rural areas and 10.3 per 1000 in studies in urban areas (range 2.8–37.7). The corresponding figures for active epilepsy were 12.7 per 1000 (range 3.5–45.4) and 5.9 per 1000 (range 3.4–10.2)².

Characteristics of epilepsy in a general population

Based on a prevalence rate of 6 per 1000, it has been estimated that in the UK there are about 96,000 people with epilepsy who require continuing hospital-based medical treatment. Of those, 15,000 will have more than one major seizure a month and 36,000 more than one seizure a month. Overall it has been estimated that there are approximately 12,000 patients with severe epilepsy and additional handicaps who may require institutional care.

In population-based studies the most frequent causes of epilepsy are cryptogenic (presumed symptomatic) or idiopathic (presumed genetic), ranging from 44.5%³⁴ to 67%³⁵, with the proportion of identified causes (symptomatic or localisation-related epilepsy – remote or progressive) increasing with age. The number of cases classified as cryptogenic has remained broadly similar over the past 20 years despite significant improvements in neuroimaging. In a study in New York³³ 55% of cases were defined as idiopathic/cryptogenic, similar to the 61% of cases in the NGPSE⁶ almost 20 years ago. Risk factors or associated factors linked to the subsequent development of epilepsy such as cerebrovascular disease, head trauma, neurodegenerative disease, CNS infections, neoplasms and learning disability predominate in identified aetiologies in population-based incidence studies. Aetiologies tend to be age specific with cerebral palsy, congenital brain damage and learning disability predominating in the young, while tumours, neurodegenerative disorders and especially cerebrovascular disease dominate in the elderly. In resource-poor countries, infective causes (e.g. parasitic infestation, malaria, tuberculosis) are an important risk factor for epilepsy. However, as in developed countries, cryptogenic cases predominate.

Based on community-based studies^{6,12,36}, proportions (%) of presumed identified causes of epilepsy are the following: cerebrovascular disease 11–21%, trauma 2–6%, tumours 4–7%, infection 0–3%, and idiopathic 54–65%.

Partial seizures predominate in most studies from developing countries: NGPSE (59% vs 39%)⁶, the Rochester study (57% vs 40%)¹², the Umeå study (Sweden) (68% vs 16%)³⁶ and the CAROLE study (France) (46.2% vs 31.9%)³⁷. A systematic review¹⁷ found that partial seizures occurred in 55% of patients compared to 45% with generalised seizures. In the Rochester study age-specific incidences of generalised and partial seizures were compared; generalised seizures were more common in the first five years of life, the incidence was similar for both between the ages of 6 and 24, and partial seizures were at least twice as common as generalised onset seizures in adults over 24 years¹². Interestingly, a predominance of partial seizures has also been demonstrated in a community-based study of children with newly diagnosed epilepsy (55% had partial seizures compared to 45% with generalised seizures)³⁸.

In contrast, many studies from the resource-poor countries have found more people with generalised seizures (80.5% in Pakistan and 65.4% in Turkey)³⁹. The combined use of EEG and clinical data allows the reclassification of some cases clinically diagnosed as generalised seizures to partial seizures with secondary generalisation, as was shown in a study from Bolivia⁴⁰. Two-thirds of cases were clinically diagnosed with generalised seizures (34% partial seizures) but, on the basis of electro-clinical data, the proportion with partial seizures increased to 53%.

Epilepsy syndromes are classified according to the ILAE classification⁴¹, which is based on age, clinical semiology and electrophysiological findings. However many cases in epidemiological studies are unclassifiable according to the current classification⁴². A community-based study from Iceland³⁵ showed the following syndrome frequencies in the cohort (with calculated incidence rates): juvenile myoclonic epilepsy (JME) (1%; incidence 0.7 per 100,000 person years), childhood absence epilepsy (1%; incidence 0.8 per 100,000 person years), benign rolandic epilepsy (5%;

incidence 2.8 per 100,000 person years), West syndrome (1%; incidence 0.007 per 100,000 person years), Landau-Kleffner syndrome (0.4%; incidence 0.2 per 100,000 person years), benign familial infantile convulsions (0.6%; incidence 0.3 per 100,000 person years), primary reading epilepsy and benign occipital epilepsy (0.1%; incidence 0.2 per 100,000 person years), respectively (see table 1).

The use of medical services over a 12-month period has been studied in a series of 1628 prevalent cases identified randomly in a population-based survey, the cases ascertained being on antiepileptic drug (AED) therapy⁴⁵. In the prior 12-month period 28% had been seen by a specialist (and 81% had been seen by a specialist at some point), 87% had been seen by their general practitioner for epilepsy and 9% had not been seen by any doctor. In the previous 12 months, 18% had attended an accident and emergency (A&E) department and 9% had been admitted to hospital because of their epilepsy. A total of 43% had attended an A&E department and 47% had been admitted to a hospital, 2% more than 10 times, at some point because of their epilepsy. Most (65%) were on monotherapy, while 35% were on polytherapy.

Despite the fact that AED therapy is widely available, many people with active epilepsy go untreated, particularly in resource-poor countries. Reasons for this treatment gap (TG) are many and in a recent systematic review of this problem in resource-poor countries, the pooled mean of the TG prevalence was 56% (95% CI 33–100). When analysed by region, the mean prevalence of TG was 64.3% (95% CI 24.3–100) in Asia, 55.4 (95% CI 39.0–78.6) in Latin America and 48.9 (95% CI 14.3–100) in Africa. The TG was higher in rural areas (73.3; 95% CI 49.5–100) compared to urban areas (46.8; 95% CI 34.1–64.2). The principal causes identified for TG were inadequate skilled manpower in the local health service (median 70%; range 64–76), cost of treatment (median 62%; range 11–90) and unavailability of drugs (median 53%; range 18–84)⁴⁶.

Effective strategies aimed at reducing the TG in developing countries need to be identified and implemented in order to improve the prognosis of people with epilepsy living in such countries⁴⁷.

Conclusions

Further epidemiological studies should be prospective population-based incident cohort studies. Such studies should focus on the temporal changes in the incidence of epilepsy in defined populations. Furthermore, research should focus on differences (real or perceived) between people of different ethnicity and social background. This may, in turn, lead to the identification of inherent risk factors in particular sub-populations for the subsequent development of epilepsy.

Table 1. Incidences of epileptic syndromes (per 100,000 person years).

		South-West France ⁴³	Rochester, USA ⁴⁴	Iceland ³⁵
Localisation-related epilepsies	Total	15.3	34.9	18.6
	Idiopathic partial epilepsies	1.7	0.2	1.6
	Symptomatic partial epilepsies	13.6	17.2	8.4
	Cryptogenic partial epilepsies	-	17.5	8.6
Generalised epilepsies	Total	7.2	7.7	3.9
	Idiopathic	6.1	3.7	3.1
	Cryptogenic or symptomatic	1.1	1.7	0.7
	Symptomatic	-	2.3	0.1
Epilepsies with both generalised and focal features	-	1.7	0.8	
Epilepsies without unequivocal focal or generalised features	1.9	8.0	8.5	
Isolated unprovoked seizures	18.3	-	22.8	

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CHAPTER 2

Classification and terminology to organise seizures and epilepsy

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Classification schemes are crucial to facilitate diagnosis of epilepsy, communication between health professionals, and communication between professionals and people with epilepsy. Because there is not a one-to-one mapping between underlying disease and clinical phenomenology in the epilepsies, there is a need for at least two separate schemes: a classification of *seizures* (i.e. a scheme based on clinically observable phenomenology) and a classification of *epilepsies* (i.e. a scheme that considers aspects beyond seizure semiology such as age at onset, neuroimaging and genetic aspects, aetiology, and prognosis).

The International League against Epilepsy (ILAE) commission on classification and terminology has created an online manual at www.epilepsydiagnosis.org/index.html. This practical tool provides a three-tiered structure of seizure classification, epilepsy syndromes, and aetiological categories.

The ILAE established a standardised classification and terminology for epileptic seizures in 1981¹. In 2017 it revised its classification scheme for epileptic seizures^{2,3} and epilepsy syndromes⁴. The 2017 scheme is a revision of a 2010 proposal⁵. The revision was motivated by a number of factors. There were some limitations regarding seizure classification in the initial classification: some seizure types such as tonic seizures may have focal or generalised onset, lack of knowledge about the onset can make a seizure unclassifiable, and determining whether there is impaired consciousness may be difficult for non-clinicians. In addition, some important seizure types are not included in the 1981 classification. The new classification of epilepsies recognise advances in neuroimaging and genetics that have improved our understanding of epilepsy syndromes.

Both classification schemes are based on the widely accepted concept that seizures can be focal or generalised. A *generalised* seizure is conceptualised as originating within, and rapidly engaging neuronal networks, in both hemispheres (though not necessarily the entire cortex). Nonetheless, generalised seizures can be asymmetric to some extent in their clinical and EEG manifestations. A *focal* seizure is thought to arise within an area confined to one hemisphere. Focal seizures can spread within the same hemisphere, and/or to areas in the contralateral hemisphere, and evolve into a bilateral tonic-clonic seizure (i.e. adopt the semiology of a primary generalised tonic-clonic seizure). The (initial) seizure semiology in focal seizures often reflects the functional role of the cortex that is involved at the onset and early evolution of the seizure.

Objective support for this dichotomy of focal and generalised seizures is provided by EEG findings in patients with generalised and focal seizures. In generalised seizures there is immediate (within

milliseconds) EEG involvement of both hemispheres. Inter-ictal abnormalities likewise involve both hemispheres simultaneously. In focal seizures, the ictal discharge is initially confined to one hemisphere. Inter-ictal abnormalities are also confined to individual areas. An inherent limitation of both the 1981 and the 2017 scheme is that seizures are not classified by their semiologic features alone but in combination with EEG findings.

The 2017 Seizure Classification Scheme

The 2017 classification scheme recognises that many seizure manifestations can be seen in seizures of both focal and generalised onset (Figure 1)^{2,3}. It also allows more flexibility to classify seizures according to the amount of detail available. Seizures are categorized according to their initial clinical manifestations as focal onset, generalised onset or unknown onset (if the onset of the seizure was not observed).

Focal (onset) seizures

Focal onset seizures are optionally further classified according to *level of awareness* and *motor manifestations* at the onset. The level of awareness during a seizure can only be judged if the person is assessed during the seizure. Retained awareness means that the person is aware of self and environment during the seizure. The term '*focal aware seizure*' corresponds to the term 'simple partial seizure' in the 1981 classification (Table 1, Table 2). Impaired awareness during any part of the seizure renders it a '*focal impaired awareness seizure*', corresponding to the term 'complex partial seizure' in the 1981 classification. The term secondary generalised tonic-clonic seizure has been replaced by 'evolving to bilateral tonic-clonic seizure'.

Motor manifestations of focal seizures

Motor manifestations at the onset of focal seizures are optionally further classified as automatisms, hyperkinetic, atonic, clonic, myoclonic, tonic or epileptic spasms if they are the predominant feature of the entire seizure.

Automatisms are coordinated repetitive movements such as chewing, licking, lip smacking, fumbling, laughing or crying that may appear somewhat purposeful but out of situational context.

Hyperkinetic manifestations are proximal, ballistic like movements such as thrashing and kicking.

A *myoclonic jerk* is a brief contraction of a muscle or a muscle group. A myoclonic jerk generated in the cortex can be distinguished from subcortically generated movements by its brief duration (usually less than 50 msec).

Clonic movements are those generated by repetitive rhythmic stereotypical jerks.

Tonic movements are characterized by sustained stiffening of a muscle or a muscle group.

Atonic behavior reflects the sudden loss of tone in a muscle or a muscle group.

Epileptic spasms are a seizure type that occur in infancy. It is characterised by tonic flexion of the head, neck and trunk with circumflexion of the upper extremities. It is usually seen in infants with extensive brain abnormalities (e.g. diffuse tuberous sclerosis). Epileptic spasms can be seen in children with gross structural lesions confined to one hemisphere, and surgical treatment can be curative in this setting, implying a focal aetiology in at least some cases.

Nonmotor manifestations of focal seizures

Nonmotor features that may characterise focal onset seizures are autonomic alterations, behavioral arrest, cognitive disturbances, emotional features, or sensory experiences.

Brief *behavioral arrest* is a common feature at the onset of a seizure and should be used to classify the seizure only when it is the predominant feature of the entire seizure.

Autonomic alterations seen in seizures are gastrointestinal sensations such as nausea, a sense of heat or cold, flushing, piloerection, palpitations, respiratory changes, or sexual arousal.

Cognitive disturbances may present as deficits in language or other higher cortical functions, or as hallucinations, illusions, forced thinking, *deja vu* and *jamais vu* experiences. Impairment of awareness does not classify a seizure as a cognitive (impaired) seizure, since impairment of awareness can be seen in any focal seizure.

Emotional features present in focal seizures are anxiety, fear, agitation, anger, pleasure, joy, laughing (gelastic) or crying (dacrystic).

Autonomic, cognitive and emotional features may be subjective experiences only and/or visible to the observer.

Sensory phenomena experienced during seizures are somatosensory, olfactory, gustatory, vestibular or elementary visual or auditory sensations.

As with the motor features listed above, nonmotor manifestations should be used to classify a seizure only if they are the most prominent feature of the seizure.

Lastly, it is recognised that a focal onset seizure may evolve to a *bilateral tonic clonic seizure*, which at this point may be indistinguishable from a primary generalised tonic clonic seizure.

The 2017 seizure classification scheme does not recognise any other semiological sequences but suggests that a seizure be classified by its most prominent features.

Generalised (onset) seizures

Generalised seizures are defined as seizures that involve a bihemispheric network from the onset. They are further classified into those with prominent *motor features* and those with *nonmotor features* with the leading symptom loss of awareness, for which the term 'absence' is used. The 1981 classification for generalised seizures has been gently expanded to recognise combinations of myoclonic, tonic, clonic and atonic seizures as well as myoclonic absence seizures and eyelid myoclonia.

Generalised motor seizures

In a *generalised tonic clonic seizure*, a tonic contraction of the extremities and axial trunk muscles is the initial manifestation, resulting in extension of the neck and extension of the extremities. The tonic contraction of the diaphragm and abdominal and chest wall muscles against the contracted glottis causes the characteristic tonic cry. The patient may become cyanotic during this phase. The generalised tonic activation is only sustained for a short period of time. The contractions become progressively longer and interrupted, resulting in clonic jerking of the extremities. There may be reflectory emptying of the bladder and bowels, and the patient may bite their tongue. There are variations on this theme: the tonic or the clonic phase may be skipped (generalised clonic or generalised tonic seizures), and asymmetric features (e.g. forced head turn to one side, or

asymmetric or asynchronous jerking) can be seen. After the seizure, the patient is in a deep coma and it usually takes 15–60 minutes to regain consciousness. Patients often feel utterly exhausted and report diffuse muscle aches, headache or depressed mood for up to several days after a generalised tonic-clonic seizure.

Generalised *myoclonic-tonic-clonic seizures* begin with a few myoclonic jerks followed by tonic-clonic activity. These seizures are commonly seen in patients with juvenile myoclonic epilepsy and occasionally with other generalised epilepsies.

A *myoclonic-atonic seizure* involves brief jerking of limbs or trunk, followed by a limp drop. These seizures, previously called myoclonic-astatic seizures, are most commonly seen in Doose syndrome but can also be encountered in Lennox-Gastaut and other syndromes.

Generalised atonic seizures are characterised by a sudden generalised loss of tone. This may manifest as a head drop or, if the patient is standing, as a forward fall that the patient cannot mitigate, often resulting in head and facial injuries.

Absence (generalised nonmotor) seizures

Typical absence seizures are characterised by a behavioural and mental arrest for a few seconds. After the seizure, the patient resumes their activity as if nothing had happened. Absence seizures may be associated with subtle jerky movements of facial or truncal muscles. However, the lapse of awareness with immediate post-ictal recovery is the characteristic feature. The typical absence seizure is seen in developmentally normal subjects and associated with rhythmic 3Hz spike and wave complexes in the EEG.

Atypical absence seizures are typically seen in patients with developmental delay. The behavioural arrest may be longer, may be associated with loss of tone and it may be more difficult to ascertain the arrest as such, compared to the patient's behaviour at baseline. The EEG in these patients usually shows background abnormalities (diffuse slowing) and the spike and wave complexes are of less than 3 Hz in frequency.

A *myoclonic absence seizure* refers to an absence seizure with rhythmic three-per-second myoclonic movements, causing ratcheting abduction of the upper limbs leading to progressive arm elevation, and associated with three-per-second generalized spike-wave discharges. Duration is typically 10–60s. Impairment of consciousness may not be obvious. Myoclonic absence seizures occur in a variety of genetic conditions and also without known associations.

Eyelid myoclonia are myoclonic jerks of the eyelids and upward deviation of the eyes, often precipitated by closing the eyes or by light. Eyelid myoclonia can be associated with absences but also can be motor seizures without a corresponding absence, making them difficult to categorize. Absence seizures with eyelid myoclonia and EEG paroxysms induced by eye closure and photosensitivity constitute Jeavons syndrome.

Classification of epilepsies⁴

The ILAE 2017 classification of epilepsies (as opposed to seizures) provides a 3-tiered framework. The first stage is diagnosis of *seizure type* as described above (Figure 2). Following this, the next step is of *epilepsy type: focal* (including multifocal), *generalised*, *combined focal & generalised* and *unknown*. A patient's epilepsy type can be classified into one of these categories by knowledge (or lack thereof) of seizure types and supported by interictal EEG findings. An example in which both focal and generalised seizures occur is Lennox-Gastaut syndrome. The third level is that of *epilepsy*

syndrome that also takes into account clinical, EEG and imaging factors along with co-morbidities such as intellectual or psychological dysfunction. In some cases, where the clinician is unable to make a syndromic diagnosis, the epilepsy type may be the final level of diagnosis.

The 2017 classification of epilepsies emphasises the importance of determining the *aetiology* of the patient's epilepsy. It recognises six aetiological categories: *structural*, *genetic*, *infectious*, *metabolic*, *immune* and *unknown*. Importantly, these categories are non-exclusive. For example, a patient with tuberous sclerosis has a genetic aetiology (mutation in the TSC1 or TSC 2 gene encoding hamartin and tuberin), resulting in the structural abnormal tubers.

Structural aetiology: An abnormality is visible on structural neuroimaging with reasonable inference that this is the cause of the patients seizures. These may be acquired (trauma, stroke and infection) or genetic such as many malformations of cortical development. Hippocampal sclerosis is a common imaging finding that causes mesial temporal lobe seizures and gelastic seizures are associated with hypothalamic hamartoma. When there is a structural abnormality, this highlights the need for consideration for epilepsy surgery should the patient fail medical therapy.

Genetic aetiology: There is a known or presumed genetic mutation causing seizures, which may be part of a wider disorder. In the majority of cases, the underlying genes are not yet known. The inference of a genetic aetiology may be based solely on a family history of an autosomal dominant disorder e.g. Autosomal Dominant Nocturnal Frontal Lobe epilepsy, where the underlying mutation is known in only a small proportion of individuals at this time. In some epilepsy syndromes, it is inferred from population and familial aggregation or twin studies e.g. Childhood Absence Epilepsy or Juvenile Myoclonic Epilepsy. In these cases there is thought to be polygenic inheritance. Rarely a single mutant gene or copy number variant of major effect is identified, though this is increasing with advances in molecular genetics. The best known example is Dravet syndrome in which >80% of patients have a pathogenic variant of SCN1A; this has implications for treatment (stiripentol is effective in these patients). Of note, genetic does not equate with inherited; an increasing number of de novo mutations are being identified in both severe and mild epilepsies.

Infectious aetiology: The epileptic disorder results directly from an infection and refers to a patient with epilepsy following an infection rather than with seizures occurring in the setting of acute infection such as meningitis or encephalitis. This is the most common aetiology worldwide. Common examples include neurocysticercosis, tuberculosis, HIV, cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis and congenital infections such as Zika virus and cytomegalovirus. These infections sometimes have a structural correlate.

Metabolic aetiology: The epilepsy results directly from a known or presumed metabolic disorder in which seizures are a core symptom of the disorder. It is most likely they will have a genetic basis. It is important to seek to identification the specific metabolic cause due to implications for specific therapies and potential prevention of intellectual impairment. Examples are porphyria, uremia, aminoacidopathies or pyridoxine-dependent seizures.

Immune aetiology: There is evidence of an autoimmune-mediated central nervous system disorder and that seizures arise as a result of this. The earliest identified autoimmune encephalitis associated with seizures were anti-NMDA (N-methyl-D-aspartate) receptor encephalitis and anti-LGI1 encephalitis. However, this field is rapidly expanding with identification of new antibodies and greater access to antibody testing. Identification is important due to treatment implications with targeted immunotherapies.

Unknown aetiology: In these cases the cause of the epilepsy is not yet known.

Comorbidities: Many of the epilepsies are associated with comorbidities such as learning difficulties/intellectual disability, psychiatric features such as autism spectrum disorders and depression, and motor deficits such as in cerebral palsy. These should be considered for every patient at each stage of classification.

Idiopathic/genetic generalised epilepsies

The old term 'idiopathic' generalised epilepsy has been replaced by 'genetic' due to a presumed genetic predisposition though 'idiopathic' is still an accepted term. Amongst the (idiopathic, genetic) generalised epilepsies, four syndromes are well recognised: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and generalised tonic clonic seizures only.

Developmental and epileptic encephalopathy

An *epileptic encephalopathy* is defined as a condition where the epileptic activity (as detected on EEG) in itself contributes to severe cognitive and behavioural impairment. This implies that amelioration of the epileptiform activity may improve the developmental consequences. However, many of these conditions have developmental consequences arising directly from their genetic etiology, irrespective of the effect of frequent epileptic activity on development. Therefore, the term '*developmental and epileptic encephalopathy*' is used in the new classification.

Pharmacoresponsive and self-limiting epilepsies

Since so-called 'benign childhood epilepsies' such as BECTS (benign epilepsy with centrotemporal spikes) can have transient or longer lasting cognitive effects, this term has been replaced by 'self-limited' - referring to spontaneous resolution of a syndrome - and 'pharmacoresponsive', meaning that the syndrome is likely to be controlled with appropriate medications.

Status epilepticus

Seizures are almost always self-limiting. Rarely one may follow another in close succession (without complete recovery in between seizures) or the ictal activity may be ongoing. Status epilepticus has been traditionally defined as ongoing seizure activity for 30 minutes or more. However, most seizures self-limit within five minutes or less. From a pragmatic point of view, a seizure that lasts longer than five minutes often warrants pharmacological intervention. Any seizure type listed in Tables 1 and 2 may occur as status epilepticus. Status epilepticus is covered in more detail in Chapters 33 and 34.

Convulsive status

This is a state of recurrent tonic-clonic seizures without recovery of consciousness between attacks. It represents a medical emergency with a high morbidity and mortality. Status may occur in approximately 3% of people with epilepsy but it is most common in patients with severe epilepsy who are non-compliant with drug therapy. It may also occur in alcohol withdrawal, in acute meningitis or encephalitis, and in acute metabolic disturbances.

Nonconvulsive status

This term is used imprecisely for the following two very different scenarios:

- a) Motor manifestations in convulsive status inevitably cease at some point. However, the cerebral cortex may continue to generate ictal discharges ('no longer convulsive status epilepticus'). This represents the most severe form of status, with ongoing excitotoxicity on a cellular level and high morbidity and mortality from a clinical perspective.

- b) Ictal activity that from the onset was not associated with motor manifestations. Usually the leading symptom is a change in the patient's cognitive state (confusion, disorientation with subsequent amnesia). This kind of status epilepticus is thought to have focal origin, though this may no longer be evident once the ictal activity has been ongoing.

Focal status

The ongoing seizure activity that defines status epilepticus may be restricted to a confined brain area. In this setting the ictal symptoms reflect the cortical area affected (e.g. aura continua, aphasia). One classic example is *epilepsia partialis continua* which refers to repetitive jerking of muscles or muscle groups in the face, arm or leg and which was originally described in association with epidemic encephalitis in Russia. Nowadays, the most common aetiologies are vascular disease, Rasmussen encephalitis, and tumours.

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ILAE 2017 Classification of Seizure Types Expanded Version ¹

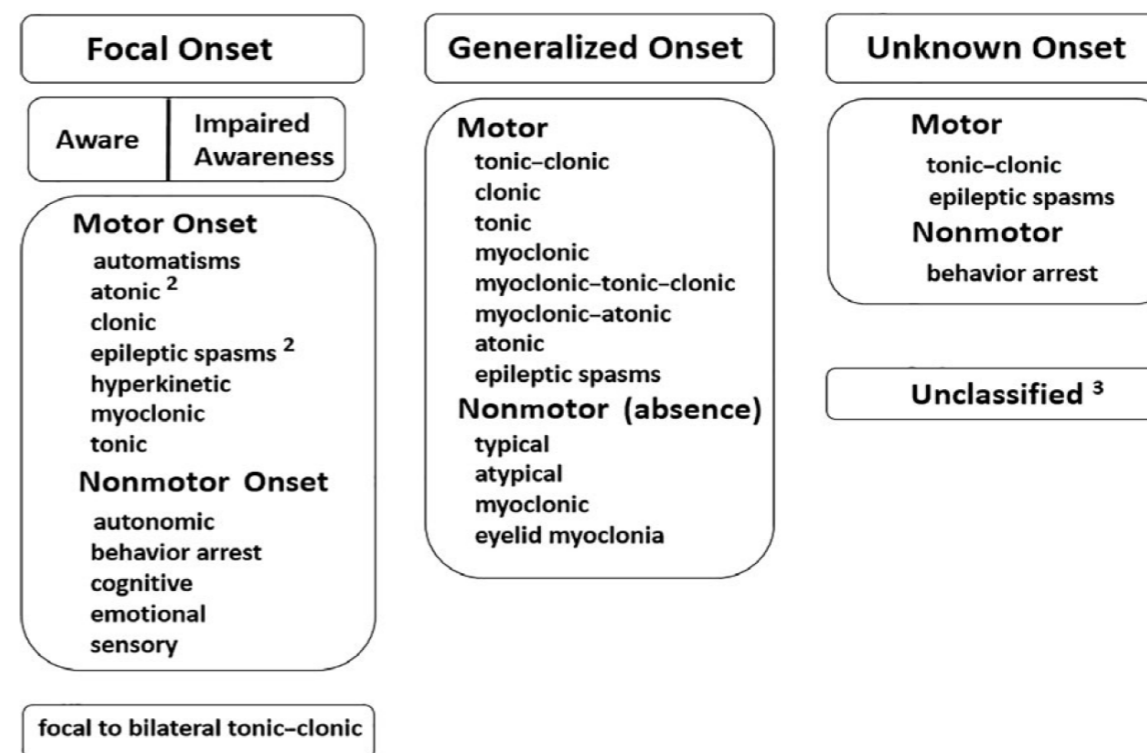


Figure 1. ILAE 2017 Classification of Seizure Types³

Table 1. ILAE 1981 International classification of seizure¹

Partial seizures	Generalised seizures
Simple (consciousness not impaired) <ul style="list-style-type: none"> • With motor symptoms • With somatosensory or special sensory symptoms • With autonomic symptoms • With psychic symptoms 	Absence seizures <ul style="list-style-type: none"> • Typical • Atypical
Complex (with impairment of consciousness) <ul style="list-style-type: none"> • Beginning as simple partial seizure (progressing to complex seizure) • Impairment of consciousness at onset <ul style="list-style-type: none"> a) Impairment of consciousness only b) With automatism 	Myoclonic seizure Clonic seizures Tonic seizures Tonic-clonic seizures
Partial seizures becoming secondarily generalised	Atonic seizures

Table 2: Differences in the 1981 and 2017 seizure classification schemes

1. The term 'partial' has been changed to 'focal'.
2. Certain seizure types can be either of focal, generalised or unknown onset.
3. Seizures of unknown onset may have features that can still be classified.
4. Awareness is used as an optional classifier of focal seizures.
5. The terms dyscognitive, simple partial, complex partial, psychic and secondarily generalized were eliminated.
6. New focal seizure types include automatisms, autonomic, behavior arrest, cognitive, emotional, hyperkinetic, sensory, and focal to bilateral tonic clonic seizures. Atonic, clonic, epileptic spasms, myoclonic and tonic seizures can be either focal or generalised.
7. New generalised seizure types include absence with eyelid myoclonia, myoclonic absence, myoclonic-tonic-clonic, myoclonic-atonic, and epileptic spasms.

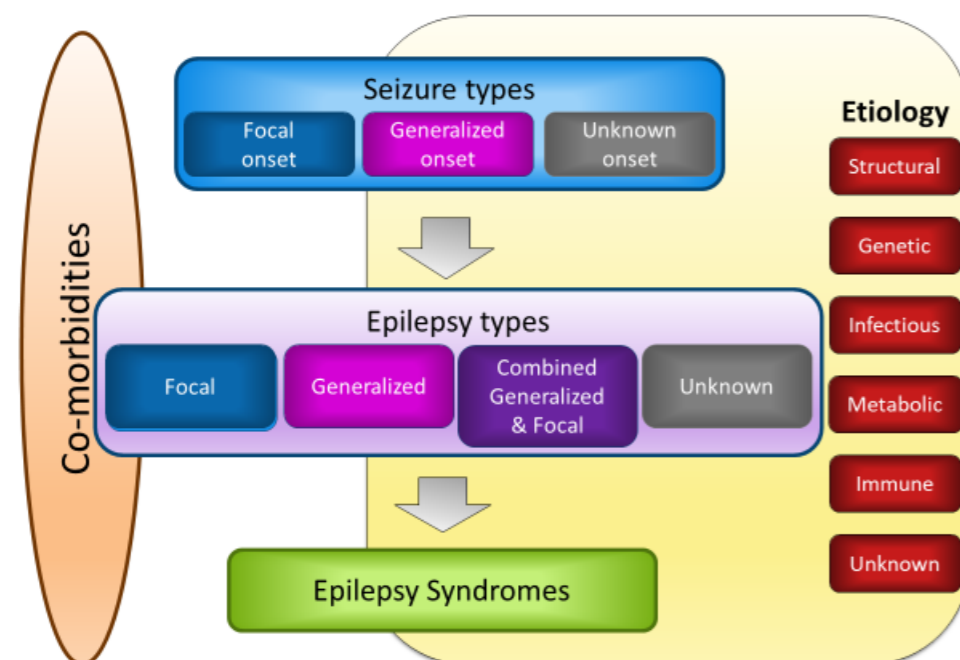
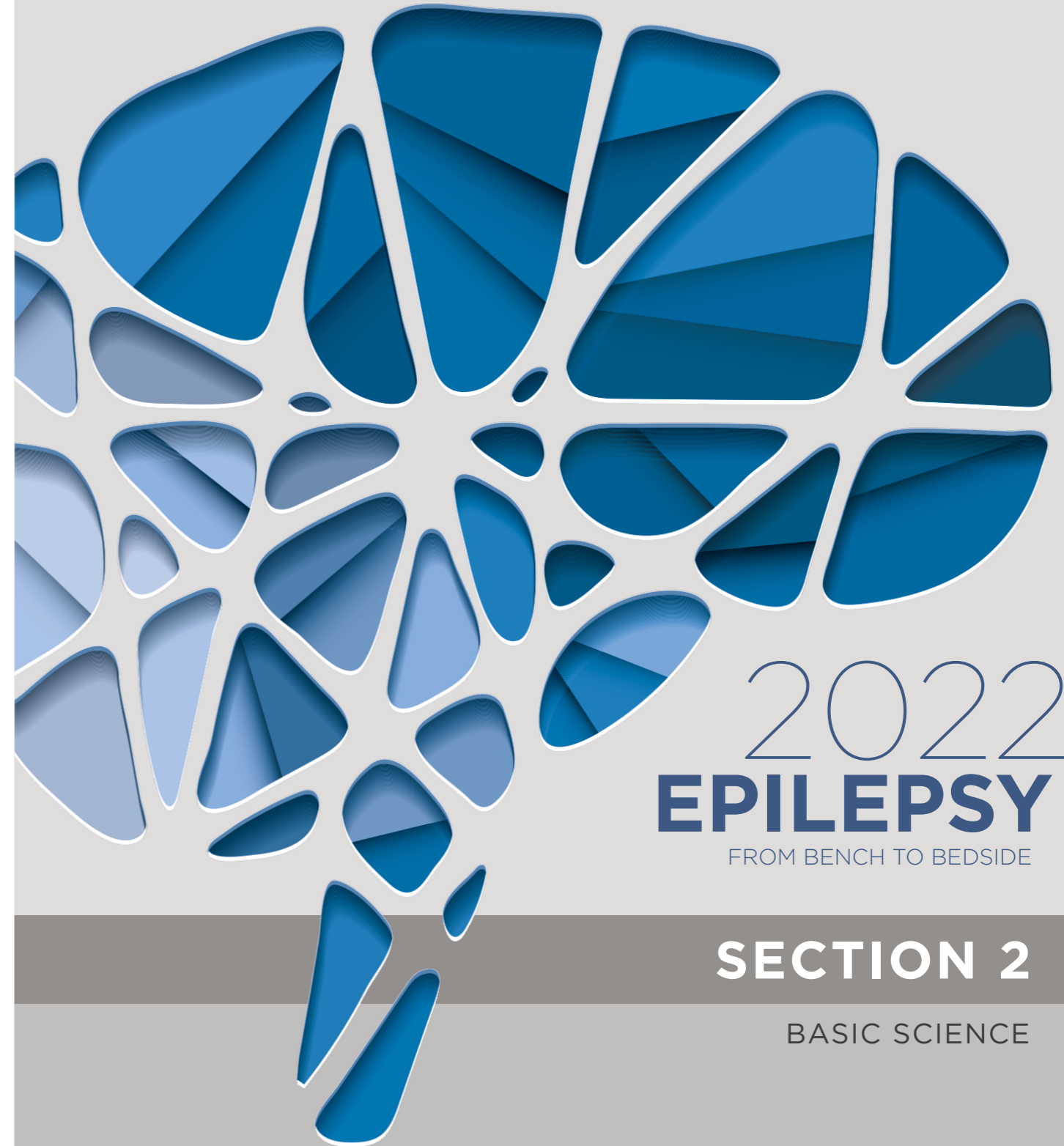


Figure 2: 2017 Classification of Epilepsy Syndromes⁴



CHAPTER 3

Basic mechanisms of epilepsy

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Epileptic seizures typically involve excessive firing and synchronisation of neurons, usually for periods of tens of seconds to minutes. This interrupts the normal working of the parts of the brain involved, leading to the clinical symptoms and semiology of the specific type of epilepsy. This chapter will outline basic mechanisms of epileptic discharges, particularly in terms of the cellular electrophysiology of focal epilepsies. It will outline recent advances in clarifying the concept of 'hypersynchronous' neuronal activity during seizures.

Focal epileptic activity

Focal epilepsies arise in the neocortex and limbic structures including hippocampus and amygdala. Work on a range of experimental models produced detailed theories on the generation of brief (~100-500ms) epileptic events analogous to the 'inter-ictal spikes' often found in the EEGs of people with focal epilepsy. Experimental inter-ictal discharges are characterised by abrupt 'paroxysmal' depolarisation shifts (PDSs) that occur synchronously in the majority of neurons in the local area. These are large depolarisations, 20-40 mV, which make the neurons fire rapid bursts of action potentials. The PDS has properties of a giant excitatory postsynaptic potential (EPSP), and depends on glutamate, which is the main excitatory synaptic transmitter in the brain. This giant EPSP is driven by the simultaneous excitation from many other neurons within the same population. The PDS also depends on the intrinsic properties of the soma-dendrite regions of the neurons, for instance voltage-sensitive calcium channels can produce slow depolarisations that drive multiple fast (sodium channel) action potentials.

Combined experimental and theoretical work on many experimental models show that the following features are sufficient for this kind of epileptic discharge:

- Excitatory (usually pyramidal) neurons must make divergent connections into a synaptic network. The probability of such connections can be quite low – for instance between ~1-2% of randomly-chosen pairs of pyramidal cells in the hippocampus.
- The synapses need to be strong enough, because of the properties of the individual synapses and/or because of the firing patterns of the presynaptic neurons (burst firing due to slower voltage-sensitive depolarising channels means that synaptic potentials can summate). Essentially neurons need to have a good chance of driving their postsynaptic targets above threshold.

- The population of neurons must be large enough (the ‘minimum aggregate’ – analogous to the critical mass of a nuclear fission bomb). This minimum aggregate allows neurons to connect with almost all the others in the population within a few synapses, with the result that activity in a small subset of neurons can spread through the population very rapidly under the right conditions. The divergent connections mean that the neuronal population is recruited in a near-geometrical progression. In experimental models the minimum epileptic aggregate can be as low as 1000–2000 neurons, but is probably larger in human epileptic foci.

The conceptual framework of the chain reaction of excitation through networks of glutamatergic neurons was mainly developed by an iterative combination of experiments on normal brain tissue, exposed to convulsant drugs *in vitro*, and computer simulations. Given these experiments were on normal tissue (modelling symptomatic seizures rather than epilepsy), the networks responsible for the epileptic activity exist to serve the normal operations of the brain, not to cause seizures. Under physiological conditions the risk of excessive synchronisation is controlled by several mechanisms, most notably the presence of inhibitory hippocampal neurons, and come in a variety of types. Those, such as the basket cells, responsible for ‘feedback inhibition’ provide an intuitively plausible mechanism: they receive excitatory input from many pyramidal cells, are easily excited, fire action potentials at very fast rates, and inhibit many pyramidal cells. They are therefore ideally suited to detect the build-up of excitation in the pyramidal cell population and to respond by blocking the ability of those pyramidal cells to generate action potentials in response to excitatory synaptic input on their dendrites¹.

Interictal spikes come in distinct types. Even in brain slices some have a much greater GABA-ergic involvement, in which case they result in larger transient increases in extracellular potassium ions and can trigger seizure-like discharges. The difference between the primarily glutamatergic and largely GABAergic interictal spikes² may parallel distinct classes of interictal EEG spikes in people with epilepsy³.

Seizures, or seizure-like discharges in brain slices, last tens of seconds to a few minutes, much longer than interictal spikes. *In vitro*, and probably *in vivo*, they depend on sustained excitation, in part driven by increased extracellular potassium concentrations which result in pronounced DC shifts in the extracellular potential.

Other factors contribute to epileptic discharges. Networks of inhibitory neurons can have proepileptic effects under some circumstances¹: e.g. changes in intracellular chloride homeostasis can make inhibitory synaptic potentials excitatory, or in other cases synchronised inhibitory activity can boost glutamatergic excitation to trigger epileptic events. Electrotonic junctions (best evidence is between inhibitory neurons) can contribute to synchronisation and reduce seizure threshold. Electrical field or ephaptic effects produce rapid synchronisation of action potentials on a millisecond timescale by modulating local “transmembrane” potentials. Finally, glia may play active roles both through the control of extracellular ions and transmitters, and in releasing transmitters in response to activation.

Chronic epileptic foci

Epilepsy is by definition a chronic condition. Chronic epileptic foci depend on abnormal functional organisation of the neuronal networks in the region. Many epilepsies are acquired. Perhaps the clearest example is post-traumatic epilepsy, where a severe head injury has a 20–30% risk of leading to spontaneous epileptic seizures after many months to several years, both clinically and in the corresponding rat model. During the latent period, the process of ‘epileptogenesis’ takes place, which transforms normal brain networks into epileptic foci. While seizures directly triggered by the

injury over the following week or so can be blocked by current antiepileptic drugs, the process of epileptogenesis cannot. Experimental work suggests that it is possible to disrupt epileptogenesis, for instance by focal application of tetrodotoxin to silence the tissue, or administration of cannabinoid receptor antagonists. An effective treatment to prevent epileptogenesis is a major goal in current epilepsy research.

Several of the common chronic models of focal epilepsy, in particular temporal lobe epilepsy, also depend on epileptogenesis. Initial insults include several that trigger acute status epilepticus (e.g. kainic acid, pilocarpine, sustained electrical stimulation) and others that do not (e.g. kindling, intrahippocampal tetanus toxin). With the exception of kindling, which generally does not result in spontaneous seizures, these models usually have a latent period of 1–2 weeks before spontaneous recurrent seizures start, which can be interpreted as a shortened version of clinical epileptogenesis.

Cellular mechanisms in chronically epileptic tissue. A key issue is the nature of the abnormalities in the functional organisation of brain tissue which makes it prone to generate epileptiform discharges, while in most cases sustaining relatively normal activity most of the time. Chronic experimental models, and where it is possible to make the appropriate measurements in human localisation-related epilepsies, reveal multiple changes in the structure and function of the neuronal networks. Some of the better characterised include:

- Increased synaptic connectivity. The best known example is mossy fibre sprouting, where the axons of the granule cells of the hippocampal dentate area, which normally are restricted to the hilus and parts of CA3, but in temporal lobe epilepsy invade the molecular layer above the granule cell body layer. Other axons are more difficult to assess, but sprouting does occur in at least some cases. At least in theory, this will promote the chain reaction recruitment of excitatory, glutamatergic neurons outlined above, although their additional synapses onto interneurons complicate the pathophysiology.
- Intrinsic properties. Voltage-gated ion channels change in many epilepsies. This is very clear in the small minority of epilepsies that are genetic channelopathies: in some, potassium channels are weakened, in others sodium channels may become more persistent. In these cases the mutation is presumably a primary factor in epileptogenesis. Changes in voltage-gated ion channels also can be found in much more common epilepsies that do not have an obvious genetic basis, for instance temporal lobe epilepsy where sodium channel inactivation is delayed leading to increases in persistent sodium currents (often in parallel with a loss of sensitivity to carbamazepine).
- Synaptic receptors can also be abnormal in epileptic tissue. Again the inherited channelopathies have good examples of altered GABAergic receptors (tending to depress inhibitory potentials), and of changes in nicotinic receptors. Other studies of more common idiopathic epilepsies reveal alterations in expression of specific receptor subunits.
- Inhibitory transmission may be altered in more subtle ways than changes in receptors, such as: changes in chloride homeostasis (specifically chloride transporters) which can make IPSPs depolarising instead of hyperpolarising, changes in the responsiveness of interneurons to excitatory input, or selective losses of particular classes of interneuron.

Inter-ictal discharges versus seizures. While inter-ictal discharges are commonly associated with localisation-related epilepsy, they are probably generated by different, or at least non-identical, circuits from those responsible for seizure initiation. Moreover, the role of inter-ictal discharges in seizure generation is far from clear. Results from some experimental models suggest that they may help prevent prolonged seizures getting started, by mechanisms yet to be determined.

Other studies suggest that inter-ictal discharges may come in more than one variety, some of which tend to precipitate seizures; these seizure-promoting inter-ictal discharges typically have a large GABAergic component and lead to relatively large increases in extracellular potassium concentrations, maybe prolonging the epileptic activity into the early stages of a seizure. However, much remains to be discovered on the precise mechanisms that sustain seizures, and that usually terminate them within a couple of minutes.

Hypersynchrony. The long-standing concept of epileptic seizures as hypersynchronous events has been challenged. One issue is the definition of synchronous: the Oxford English Dictionary version is 'existing or happening at the same time'. The criticism here is that not much in biology happens at exactly the same time. Other terms may be more precise but are not in widespread use, so a degree of imprecision in the use of language may be appropriate, at least for the time being.

The more important question is whether neurons fire synchronously, or at least within short periods of each other, during seizures. Recordings of single neurons during seizures in humans have shown surprisingly little change in firing rates. Multichannel depth recordings have shown dissociation between the widespread synchronous EEG, which is primarily generated by synaptic currents, and very localised migrating areas of increased and hypersynchronous firing of neurons. Work on experimental models in brain slices *in vitro* suggests that this dissociation is largely due to the strength of inhibitory neurons in restraining the advancing front of neuronal hyperactivity, a process which generates large field potentials (or EEGs). This spatial dissociation of EEG from neuronal firing is intriguing for fundamental pathophysiology but also has potential implications for determining the epileptogenic zone^{4,5}.

Histopathology. Epileptic foci are often associated with focal lesions. It is clear that prolonged seizures cause neuronal death, which is why those chronic models of temporal lobe epilepsy that depend on an initial status epilepticus generally are associated with substantial losses of neurons. Excitotoxicity that results from the accumulation of intracellular calcium is in large part due to prolonged activation of glutamate receptors, notably the NMDA variety. What is less clear is how repeated brief seizures cause lesions in some individuals.

High frequency oscillations

The classical EEG stops at 80-100 Hz, but work over the past couple of decades has shown that important insights can be gained from much higher frequencies. These high frequency oscillations (or activity) are often divided into sub-bands, notable ripples and fast ripples, with a demarcation at 200-300 Hz (the precise value differs between different studies). Ripples can be seen during some normal physiological states, while fast ripples seem to be pathophysiological⁶.

Ripples and fast ripples (also called 'high gamma' by some authors) appear relatively soon after the initial precipitating insult, at least in some experimental models, and provide a biomarker for whether individual animals will go on to develop spontaneous seizures. They presumably result from some of the earlier changes in the process of epileptogenesis and may provide clues on the underlying cellular and molecular mechanisms.

Fast ripples may provide a valuable marker for the 'epileptogenic zone', perhaps by providing a marker for excessive neuronal firing as distinct from excessive synaptic activity (see hypersynchrony, above). The epileptogenic zone is the volume of brain tissue that needs to be removed surgically to prevent seizures. The ultimate test is whether the seizures stop when the tissue is removed. This and the other zones identified in presurgical work-up are beyond the scope of this chapter. What is relevant is the use of fast ripples as one of the methods of defining the epileptogenic zone. Our own work suggests that fast ripples can be used in (at least experimental) cases where there is no hippocampal sclerosis to provide structural evidence.

Detecting fast ripples is not straightforward. Obviously the bandwidth of the recording system needs to be high enough - in the kHz range. But the recording electrodes also are critically important. Fast ripples are best detected with intracranial, preferably intracerebral, microelectrodes. A recent study has shown that the classical clinical macroelectrodes miss most high frequency oscillations faster than 100-200 Hz. This is probably because fast ripples in particular synchronise over very short distances, of the order of a few hundred microns, so they will be attenuated to below noise when recorded with electrodes with dimensions orders of magnitude larger. Their limited spatial extent and the small amplitude of fast ripples also make them difficult to record from the scalp.

Generalised epilepsies

This chapter is centred on focal epilepsies, in part because less is known about the pathophysiology of the primary generalised epilepsies, with the exception of absence epilepsy, which will be outlined briefly here^{7,8}. It is the one class of generalised epilepsy where there is a plausible model of basic mechanisms. It differs from localisation-related epilepsy in many important respects. In particular, it arises from the thalamocortical system, depending on the properties of both cortex and thalamus. Until recently there was a consensus on the mechanisms for the classic 3 per second spike-wave activity, which depended on synchronisation of the thalamus by rhythmic activity of networks of inhibitory neurons. The rhythm was thought to arise from the interaction of inhibitory post-synaptic potentials (IPSPs) with transient low-threshold (T) calcium channels in thalamic cells. Recent evidence, especially from one of the better models of this condition, the Generalised Absence Epilepsy Rats from Strasbourg model (GAERS), suggests that the thalamic T current may not be critical. Work on this model also suggests that the frontal cortex may play a key role in initiating absence seizures, a point that contributes to blurring the distinction between localisation-related and primary generalised epilepsies.

Conclusions

The basic neurophysiological mechanisms of some forms of epileptic activity now are understood in considerable detail. However, many important issues remain, in particular on the basic mechanisms of prolonged seizures and the precise combinations of cellular pathophysiologies and pathologies in chronic foci. Identifying specific cellular mechanisms playing crucial roles here should provide useful leads for novel and selective treatments.

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CHAPTER 4

Neuropathology of epilepsy

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Surgical pathology of epilepsy

Epilepsy surgery has been established as an effective treatment option in some pharmacoresistant focal epilepsies. Following continued advances in imaging technology, structural lesions are increasingly recognised in patients with chronic focal seizures. Electrophysiological evaluation, for example surface or invasive EEG recordings, may further define the epileptogenic area prior to tissue resection in MRI-negative patients.

Types of specimens and laboratory procedure

Epilepsy surgery can generate a range of samples from large 'en-bloc' resections to smaller biopsy samples. In many centres these will be sent directly to the neuropathology laboratory fresh to further portion the sample primarily for an accurate histological diagnosis but also to enable other investigations (frozen samples, cell culture, electron microscopy) and to biobank samples for research studies where there is sufficient material and consent. Standard laboratory operating procedures are summarised in an ILAE publication¹.

The common pathologies identified in resected tissues are represented in the Figure 1. The incidence may vary between epilepsy surgical series and depending on the age group included; for example, cortical malformations are more common than hippocampal sclerosis in paediatric cohorts. In some resections (particularly if 'MRI-negative') no-specific lesion is identified and gliosis or microgliosis may be the only histology finding. In other cases, a double or dual pathology may be found.

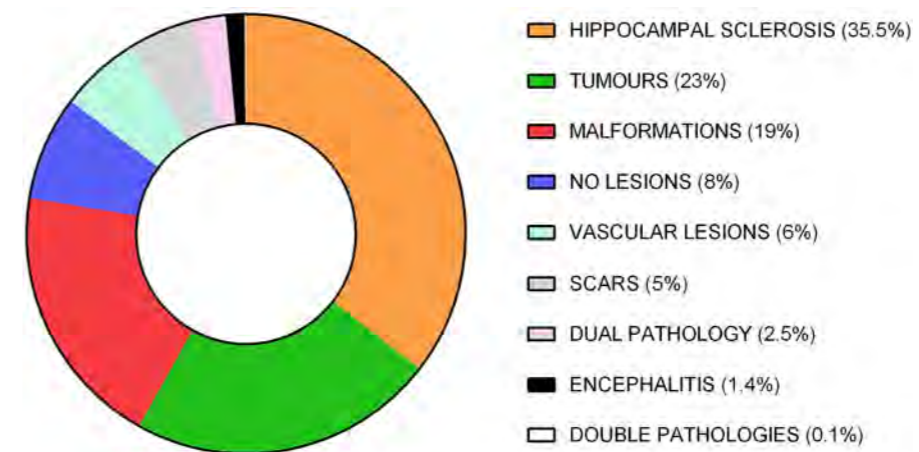


Figure 1: Main types of lesions encountered in the German Registry of 9576 Surgical Cases (The European Epilepsy Brain Bank Consortium: 20 years of interdisciplinary experience)². Dual pathology = hippocampal sclerosis plus another lesion; double pathology = two distinct pathologies (not including HS). Additional data from the European epilepsy brain bank was published in³.

Hippocampal Sclerosis

Hippocampal sclerosis (HS) is an acquired process of neuronal loss and gliosis, involving specific subfields of the hippocampus, resulting in volume reduction and hardening of this structure (sclerosis). This pathology has been recognised in patients with epilepsy for nearly 200 years, with first reports appearing in 1825 and more detailed descriptions of the pathology in a series of 90 post mortem cases, published by Sommer in 1880 (as reviewed in⁴). Pathological descriptions of HS in some of first the patients undergoing temporal lobe surgery for epilepsy treatments were published in the 1950s by Cavanagh and Meyer⁵.

Hippocampal sclerosis can be macroscopically evident at post mortem examination with unilateral (or sometimes bilateral) atrophy of the hippocampus and corresponding expansion the temporal horn of the lateral ventricle. In a typical surgical temporal lobectomy specimen carried out for epilepsy treatment, the hippocampus appears small on coronal sectioning as well as firm in texture.

The pathological diagnosis of HS is usually straightforward in standard ('H&E') sections and based on the identification of pyramidal neuron loss and gliosis affecting specific subfields, primarily CA1, CA4 and CA3 subfields. The depletion of pyramidal cells in these regions may be complete, with only sparse pyramidal and horizontal, interneuronal-type cells remaining. Severe neuronal loss is accompanied by the presence of a dense, scar-like fibrous gliosis, contracting the stratum pyrimidale. There is typically a sharp cut off between the preserved subiculum and a gliotic CA1. The granule cell layer and CA2 are regarded as more 'resistant' regions but patchy neuronal depletion in these areas is often evident. Conventional stains as LFB/CV and immunohistochemistry for MAP2, NeuN, GFAP may all assist in the appreciation of neuronal loss and are helpful when dealing with a fragmented or poorly orientated surgical specimen.

There have been many quantitative studies in the last decades aiming to correlate the severity and distribution of hippocampal damage with both the clinical and imaging features⁶. In addition, various grading schemes based on regional patterns of damage have been proposed. The current system widely used is the International League Against Epilepsy (ILAE) scheme, introduced in 2013, which recognises three distinct types of HS (detailed in Table 1, figure 2). There are some published series that have utilised scheme: some clinical-pathological studies have shown that type 1 HS is associated with a better outcome (number of patients rendered seizure-free) following surgical resection⁷ yet better long-term seizure-free outcomes and preserved pre-operative memory function are reported in type 2 HS^{8,9}. Other studies have not reported any associations between the pattern of hippocampal sclerosis and post-operative outcome¹⁰⁻¹³. There are also several correlative studies linking type of HS with memory and cognitive dysfunction^{10,14-17}.

Table 1. 2013 International League Against Epilepsy (ILAE) scheme.

ILAE (2013)	Type 1	Type 2	Type 3	No HS
Old terminologies	Classical; total, HS; Typical	CA1 predominant; Atypical HS	End folium sclerosis; atypical HS	End folium gliosis; 'mild' HS
Semi-quantitative assessment of neuronal loss				
CA1	2	1-2	0-1	0
CA2	0-2	0-1	0-1	0
CA3	0-2	0-1	0-1	0
CA4	2	0-1	1-2	0
DENTATE GYRUS	0-2	0-1	0-2	0-1
Relative frequency of HS types in surgical series	60-80%	5-25%	1-7.5%	~20%

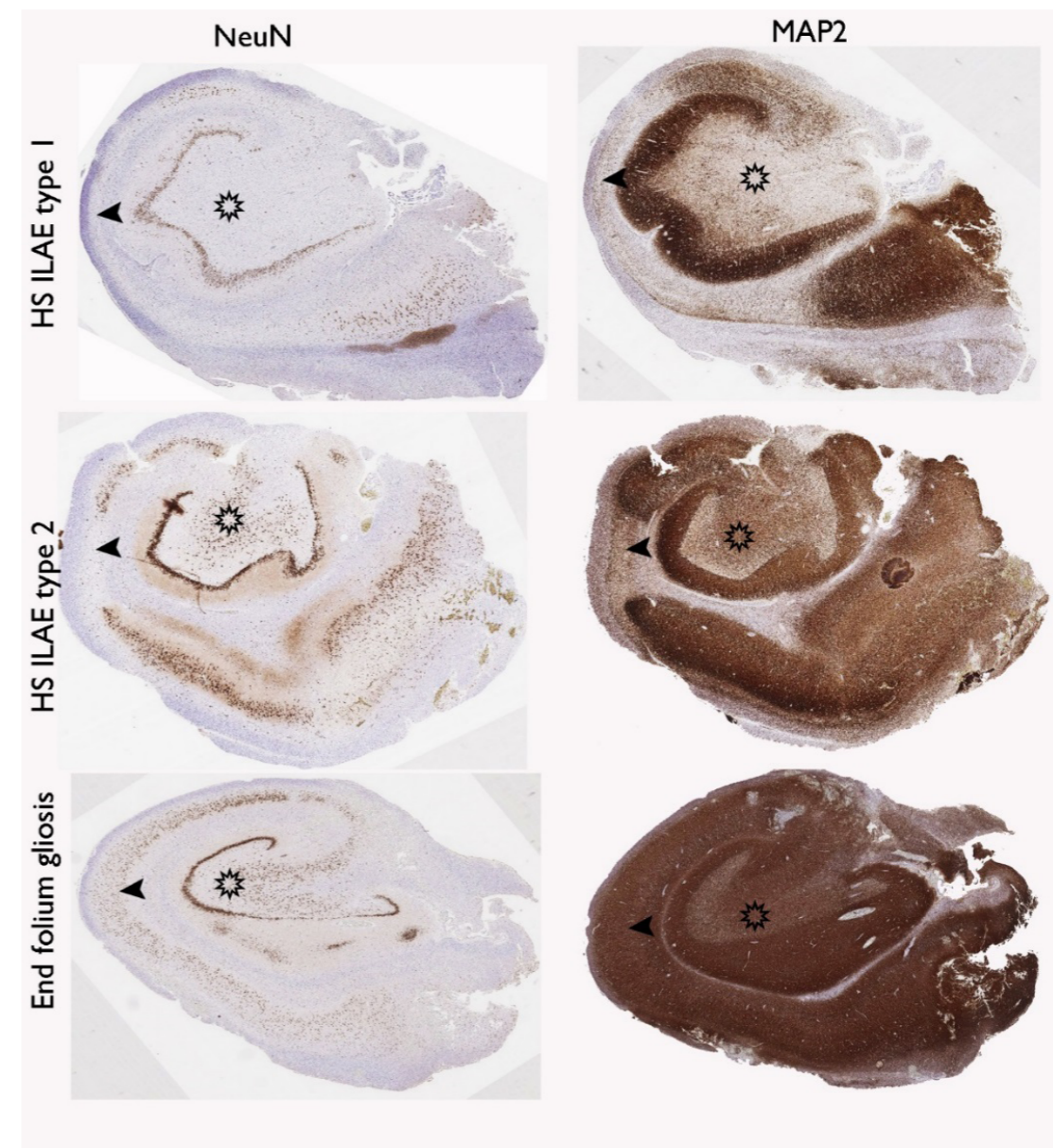


Figure 2. NeuN neuronal stain and MAP2 illustrating the pattern of neuronal loss in type 1 and type 2 HS compared to the bottom row which shows gliosis but no sclerosis (intact neurones). Star = CA4 region, CA1 region is shown with arrow.

Other pathology changes in Hippocampal Sclerosis

Tracts from prior depth electrode studies may be present, eliciting a local inflammatory and glial reaction and mild focal chronic inflammation may be present^{18,19}, evidence of extensive chronic inflammation (microglial nodules, neuronophagia) requires exclusion of underlying limbic encephalitis including viral cause^{20,21} (see section at end of chapter 'on inflammation'). Superimposed neurodegenerative changes, including phosphorylated tau accumulation in older patients with epilepsy and HS has been reported²². Regenerative and reorganizational changes, including axonal sprouting and alteration of inter-neuronal networks, occur frequently in the setting of HS in a relatively stereotypical fashion and may be relevant to the process of epileptogenesis²³. This includes alteration of interneuronal numbers²⁴⁻²⁶, cell hypertrophy, abnormal dendritic projections²⁷⁻²⁹ and

axonal sprouting. These accompanying changes can help distinguish HS in epilepsy from other causes of atrophy/sclerosis (e.g. ageing and dementia)³⁰.

Mossy fibre sprouting: Axonal sprouting in HS is exemplified by the mossy fibre pathway, the axons of the granule cells. Mossy fibre sprouting is relatively specific to epilepsy-related HS and readily demonstrated in sections with immunohistochemistry to dynorphin or Zinc-transporter 3 (Figure 3). Although the extent of mossy fibre sprouting can vary between cases it is considered to be triggered early following seizure activity although the exact mechanisms as well as its clinical significance are uncertain^{23,31}. In a recent studies the presence of mossy fibre sprouting correlated with HS type but not outcome¹³ and preserved mossy fibre pathway was associated with intact memory pre-operatively¹⁰.

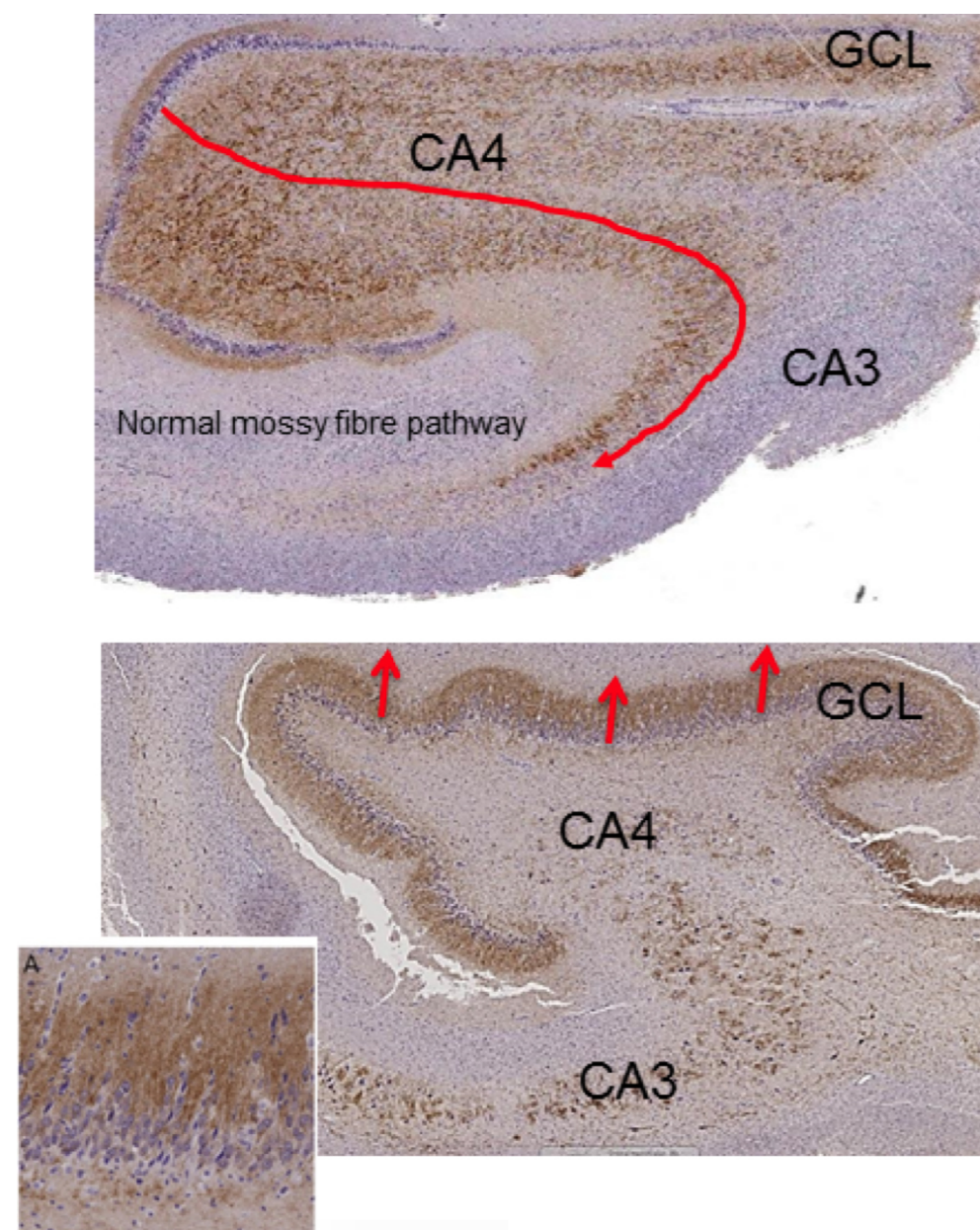
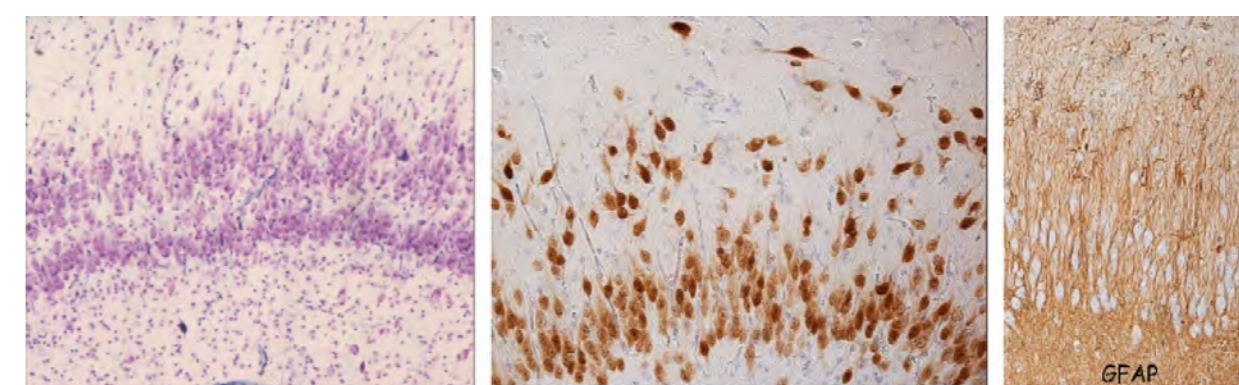


Figure 3: Top shows the normal mossy fibre pathway with ZnT3 staining and below in hippocampal sclerosis sprouting of mossy fibres into the molecular layer is shown (and in inset) and loss of the normal trajectory.

Granule cell dispersion (GCD): This alteration of the granule cell layer is present in ~40% of HS cases to significant degree. GCD typical pathological features are blurring of the outer boundary of the cell layer with the molecular layer as well as a less well-defined basal cell layer in some cases. Increased distances between individual granule cells is observed with neuropil visible between cells and an overall increased width of the cell layer up to 400 microns (compared to the normal thickness of around 120 microns). In some cases, clusters of granule cells in the molecular layer and hypertrophied cells with a more fusiform shaped cell body³² are observed. A 'bi-layer' pattern may be present in cases and GCD may alternate with stretches of neuronal loss along the dentate gyrus. Extensive GCD is virtually always seen in the context of hippocampal neuronal loss, particularly of CA4^{33,24} suggesting it is more common in ILAE type I and 3 HS. Loss of calbindin expression, particularly from the basal cells in GCD, has been reported³⁵ (Figure 4).



Patterns of Granule cell dispersion : A bilaminar pattern on the left, single dispersed neuron as seen with NeuN (centre) and the accompanying gliosis as seen with GFAP on right.

Figure 4: Patterns of Granule cell dispersion.

Pathogenesis of hippocampal sclerosis

The relationship between seizures and HS is a complex, reciprocal cause and effect model³⁶. Meyer's hypothesis of the 1950's, that an initiating insult primed an immature or 'susceptible' hippocampus for the subsequent development of HS, remains the most plausible explanation i.e. a 'two hit' model with a plethora of potential initial 'hits' including prolonged febrile seizures. With its extensive cortical connections, the hippocampus may represent the vulnerable 'fuse-box' in an immature, seizing brain. Seizures have the potential to damage the hippocampus, particularly prolonged seizures and status epilepticus. The FEBSTAT prospective study has shown that febrile status epilepticus may evolve into HS, as confirmed on MRI³⁷. HS can also arise in association with a second 'epileptogenic' pathology as a malformation or tumour ('dual pathology'). HS is typically a sporadic condition but with a complex, polygenic background and likely genetic susceptibility determinants which are still poorly understood³⁸⁻⁴²; e.g. sporadic hippocampal sclerosis and febrile seizures are linked by common genetic variation around *SCN1A* gene⁴³. In addition, epigenetic factors may contribute and specific DNA methylation profiles have recently be defined in HS⁴⁴, abnormal expression of miR-218 and miR-204 in HS⁴⁵ as well as differential miRNA expression reported in HS with or without GCD⁴⁶. Recent gene-expression studies mat shed light on molecular mechanisms and pathways involvement in HS⁴⁷. There have also been several reports of hippocampal developmental abnormalities predisposing to HS⁴⁸⁻⁵². An MRI study of asymptomatic family members of patients with TLE and HS confirmed smaller, asymmetrical hippocampal volumes⁵³ and genome-wide studies have linked common genetic variants with hippocampal volume^{54,55}. Granule cell dispersion is likely

an acquired rather than developmental pathology; it is associated with early onset of epilepsy and febrile seizures (<4 years) as well as a longer duration of epilepsy³². There are two main theories: (i) neuronal ectopia of newly generated neurones following aberrant neurogenesis as an effect of seizure activity⁵⁶⁻⁶² (ii) abnormal migration of mature neurones influenced by seizures^{63,64} and local deficiency of reelin protein and reelin-expressing cells, affecting the radial glial scaffold^{63,65,66}. Loss of regenerative capacity in the dentate gyrus has been linked to memory impairment in TLE⁶⁷ highlighting the important contribution of granule cell pathology to co-morbidities in epilepsy. However, there is still ongoing controversy over the extent of post-natal and adult neurogenesis in the dentate gyrus, as highlighted in recent studies⁶⁸⁻⁷¹.

Widespread changes in association with hippocampal sclerosis in TLE

Pathology may extend beyond the hippocampus, involving adjacent structures (as well as regions connected with the hippocampus). These additional pathologies (usually neuronal loss, gliosis) may be relevant to seizure onset (and epileptogenesis), seizure networks, associated co-morbid features including neuropsychological impairment and poor outcome following surgical treatment.

Amygdala: Neuropathology studies have reported gliosis and neuronal loss in the lateral nucleus in resections of amygdala from patients with temporal lobe epilepsy, in particular the ventro-medial aspects are more severely affected. In addition, the basal nuclei, particularly the parvicellular division, may be involved. In cases with severe neuronal loss and gliosis the term ‘amygdala sclerosis’ may be applied but there is no strict definition for the extent and severity of neuronal loss for this diagnosis. Greater amygdala neuronal loss has been shown in patients with hippocampal sclerosis, although amygdala sclerosis has also been reported in isolation. Amygdala enlargement has been reported in TLE, but the underlying pathology substrate is variable and includes tumours and malformation.

Neocortex: In the temporal neocortex, loss of neurones, when present, is most apparent in mid-cortical layers with associated gliosis. Subcortical white matter gliosis, atrophy, Chaslin’s superficial cortical gliosis and increased deposits of corpora amylacea may also be prominent. Mild, focal leptomeningeal chronic inflammatory infiltrates may follow a seizure. When neuronal loss is extensive in the temporal lobe the pattern of temporal lobe sclerosis may be accompanied by reorganisational dysplasia, now termed FCD type IIIa (see section below for dysplasia) (for review of temporal lobe sclerosis see⁷²).

Thalamus: Volume reduction of the thalamus has been observed with MRI studies, as well as in post mortem and experimental studies of epilepsy, and is more closely linked with hippocampal and amygdala atrophy and TLE. Neuronal loss and gliosis may be widespread but with some evidence for greater involvement of dorsomedial nuclei⁷³. Thalamic atrophy is more often unilateral and associated atrophy of the fornix and mammillary bodies may also be seen. Proposed pathomechanisms for injury include direct effects of seizures or transneuronal degeneration via connecting pathways.

Low grade Epilepsy Associated Tumours

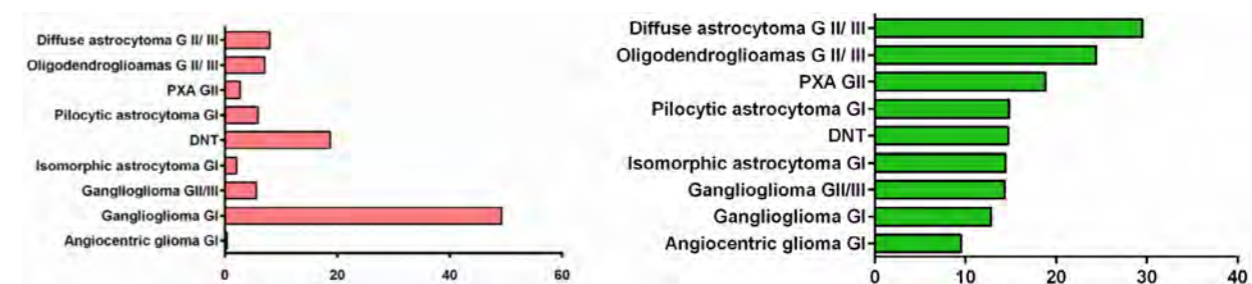
Any tumour type in the brain can cause seizures and is primarily dependent on the tumour type and location. In the setting of long-term epilepsy, specific types of low-grade tumours are more commonly found, also have been termed ‘LEATs’ (low-grade epilepsy-associated tumours). LEATs are located in the temporal lobe in ~¾ of cases, typically present in late childhood, with epilepsy as the primary and often only neurological symptom. Many LEATs represent glioneuronal tumours with a mixed cell composition and are typically low grade (WHO grade I)⁷⁴. In the revised classification of brain tumours (2016) the two main tumour types encountered are ganglioglioma

and dysembryoplastic neuroepithelial tumours/DNT⁷⁵ (see bar charts located below Table 2). However, it is acknowledged that there are deficiencies in the current classification of LEATs in terms of recognition of all subtypes, including diffusely growing tumours and that further molecular genetic characterisation of this groups is required, particularly to distinguish them from other progressive IDH1-mutant and wild type gliomas and enable correct clinical management⁷⁴. In this section DNT and Ganglioglioma tumour groups are described only (refer to WHO text book for descriptions of other entities in Table 2). Also LEATs with composite/mixed features of different tumour entities have been described (see review⁷⁶).

Table 2. WHO classification of glioneuronal tumours (1979, 1993, 2000, 2007, 2016) showing the increased recognition of glioneuronal tumour subtypes with new editions.

Tumour type	1979	1993	2000	2007	2016
Ganglioglioma GI	√	√	√ GI/II	√GI	√GI
Gangliocytoma GI	√	√	√	√	√
Dysembryoplastic Neuroepithelial Tumour GI	Not defined	√	√ (reference to non-specific form)	√ (reference to non-specific form)	√ (reference to non-specific form)
Desmoplastic Infantile Ganglioglioma/Astrocytoma		√	√	√	√
Central Neurocytoma		√ GI	√ GII	√ GII	√ GII
Extra-ventricular Neurocytoma		Not defined		√	√
Cerebellar Liponeurocytoma			√	√	√
Papillary Glio-neuronal Tumour			Not defined	√	√
Rosette Forming Glioneuronal Tumour				√	√
Multinodular Vacuolating Neuronal Tumour				Not defined	√
Diffuse Leptomeningeal Glioneuronal Tumour					√

(Note not all glioneuronal tumours cause epilepsy). GI = WHO grade 1.



Bar charts (above). The pink bar chart shows the relative incidence (%) of tumour types in epilepsy surgical series in the large European Epilepsy Brain Bank database held in Erlangen of over 1367 cases⁷⁴. Ganglioglioma and DNT are the commonest tumour types. The green bar chart shows the average age of onset of epilepsy (in years).

Dysembryoplastic Neuroepithelial Tumour (Dnt)

DNT vary in size from a few millimetres to several centimetres across; they are typically cortical based but can extend into the leptomeninges. They can be cystic on cut section. The histology is characterised by two features: a glioneuronal element and a multinodular architecture. The WHO recognises two subtypes: simple and complex forms of DNT and a 'non-specific' form is still regarded as controversial⁷⁵. The glioneuronal element is the hallmark feature of the DNT and is comprised of columns of oligodendroglial-like cells arranged along-side cortical axons and vessels with intervening mature or trapped neurones suspended in an extracellular matrix (Figure 5).

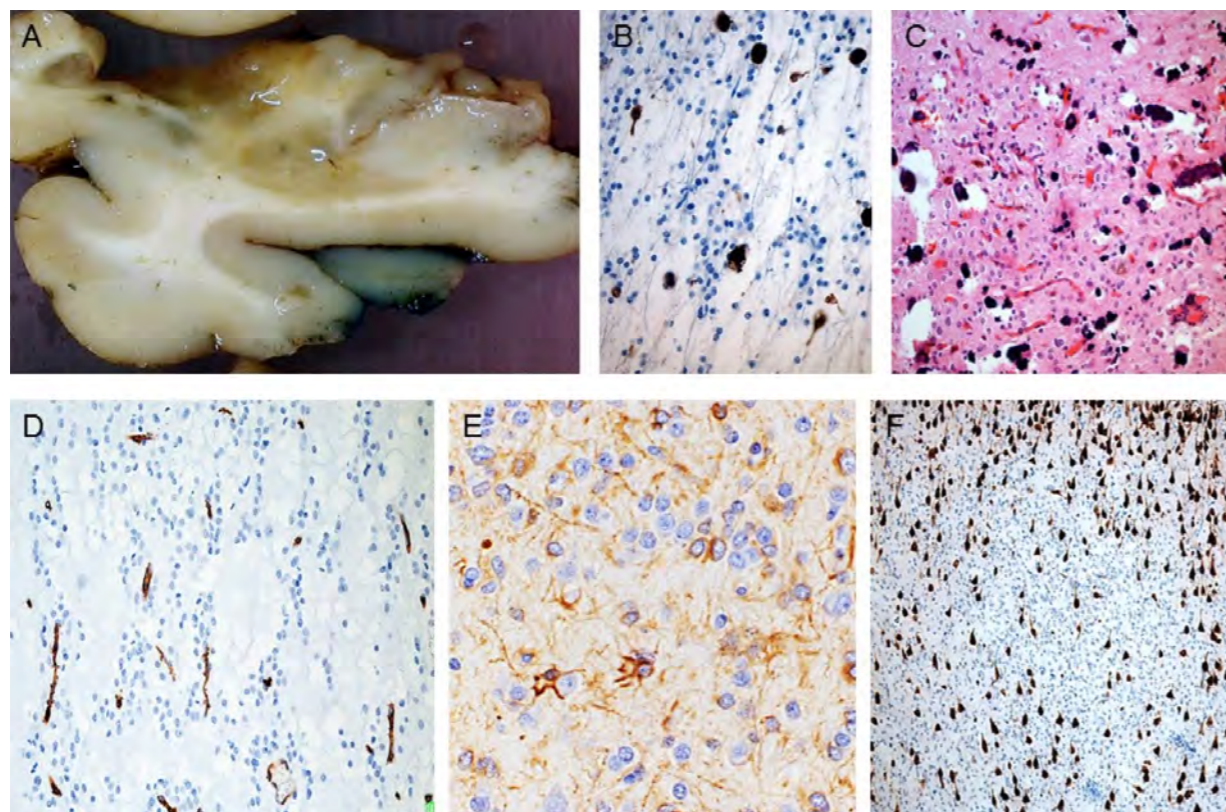


Figure 5: A. Typical macroscopic appearances of a gelatinous, cystic tumour in the temporal neocortex. B. The typical glioneuronal element is highlighted with NeuN which labels only the floating neurones and not the small tumoural oligodendroglial-like cells. C. DNT can be calcified. D. Immunohistochemistry is useful in diagnosis with CD34 typically confined to vessels and E. GFAP is often negative in the small tumour cells as is F. NeuN neuronal marker. There is no specific tissue biomarker for DNT and diagnosis relies on the growth pattern and exclusion of IDH1- positive gliomas and other LEAT types.

Immunohistochemistry and molecular testing in DNT

Immunohistochemistry is mainly directed to (i) explore neuronal versus glial differentiation and lineage and (ii) enable distinction from conventional IDH1 positive and negative gliomas as well as other CD34+ LEATs (iii) to explore mechanisms of epileptogenesis⁷⁷. Molecular testing (see section below).

Location and origins

Common sites for DNT include the temporal lobe, hippocampus and amygdala. They can extend into the ventricle. In addition there are several reports (> 45) of midline or septal DNT (see reference ⁷⁸) as well as multifocal DNT. The sites are coincidentally regions close to adult neurogenic regions which may relate to the 'dysembryoplastic' origins of these tumours.

Outcome following surgery

A recent review of DNT series showed that overall rates of seizure-freedom were around 86% with a mean age at surgery of 18 years and age of epilepsy onset of 7 years with gross total resection achieved in 79%. There is some evidence that extent of resection influences a positive outcome⁷⁹.

Tumour progression is likely to be a very rare event in DNT. Histological progression needs to be distinguished from radiological progression/enlargement which could be result of cystic degeneration or haemorrhage in residual DNT. Many patients with partially resected DNT are monitored by MRI, however, histological transformation of a grade I DNT to a higher grade tumour has been reported in only 11 cases with 8 cases of malignant transformation (WHO grade III or IV). Extra-temporal location, older age of onset, partial resections and adjuvant treatments have been cited in some cases⁷⁷. Histological review as well as molecular analysis of both primary and recurrent samples is warranted to ensure the security of the original histological diagnosis and to compare samples, as highlighted in a recent case report⁸⁰.

Ganglioglioma

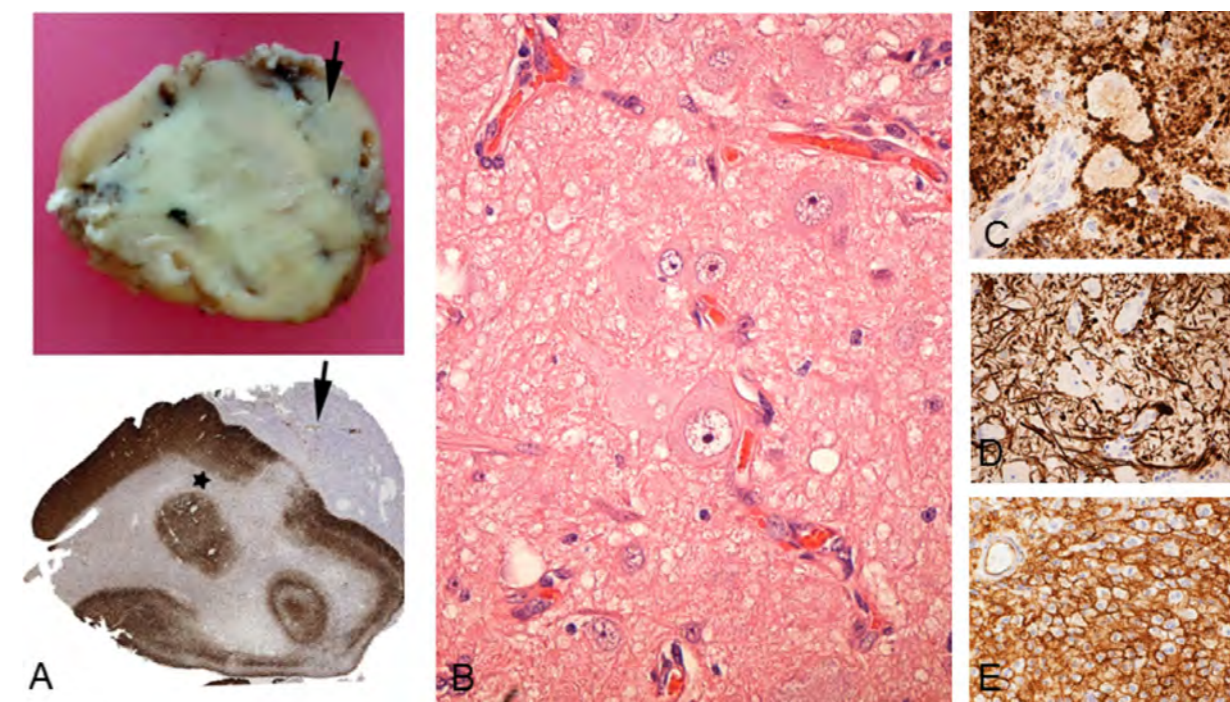


Figure 6, Ganglioglioma. The tumours can appear well defined and may extend into the meninges (arrows) (A). The hallmark histology is the presence of dysplastic neurones (B). The abnormal neurones label for neuronal markers synaptophysin (C), and the glial component for GFAP (D) and the tumour is frequently CD34 positive (E).

Ganglioglioma is the commonest type of LEAT in epilepsy series⁷⁴; it can appear well delineated macroscopically and may be solid or cystic. It has a biphasic composition of abnormally aggregated dysplastic neuronal cells (including binucleated neurones observed in around half of cases) in addition to a glial component which can vary in amount and cytological appearance (fibrillary, piloid, oligodendroglial). The main differential diagnosis is infiltration of an astroglial tumour into the cortex. Inflammation, calcification and increased reticulin are common features. Immunohistochemistry can highlight the abnormal distribution and morphology of neurones in the tumour (synaptophysin, neurofilament, calbindin, NeuN) and in around 80% CD34 expression is present⁷⁶ which can also highlight the extent of cortical infiltration by small satellite tumour nodules. Gangliogliomas are WHO grade I tumours and seizure-freedom rates post-operatively are achieved in 63-100% of patients in published series with increased extent of resections, shorter duration and younger age associated with better outcomes⁸¹. Anaplastic gangliogliomas more often arise de novo than from transformation of a low grade tumour⁸² but can also be associated with seizures and have a worse prognosis than their grade I counterparts⁸³ (see Figure 6).

Diffuse Type Glioneuronal Leats (see Figure 7)

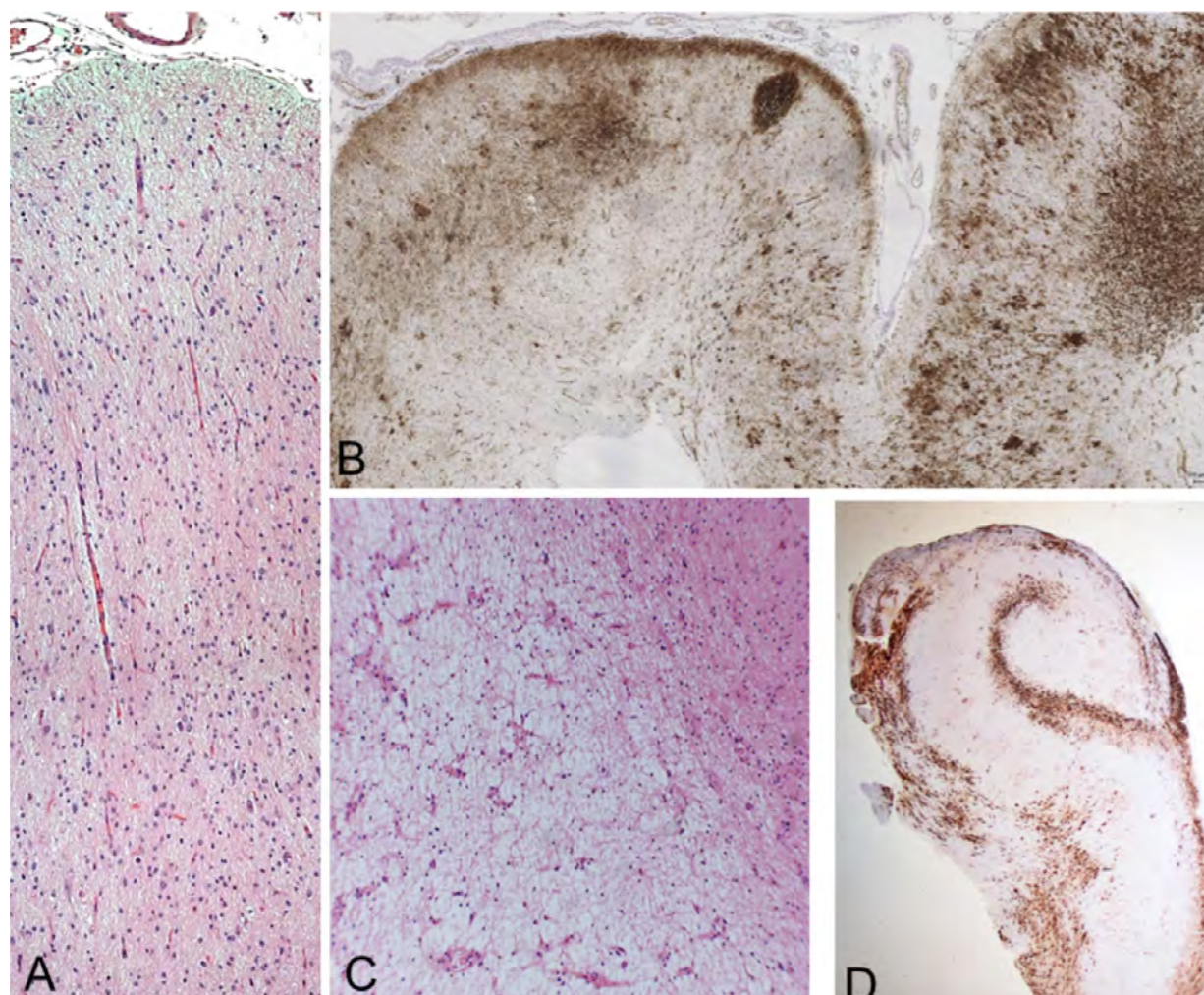


Figure 7: Diffuse glioneuronal tumours: **(A)** show a composition of oligodendroglial like cells in the cortex and lack a glioneuronal element or dysmorphic neurones. **(B)** CD34 positivity of the islands of tumour within the cortex and prominent labelling in layer I **(C)** Rarefaction of the underlying white matter (loss of axons and myelin) is a common finding and **(D)** they can involve the hippocampus as shown here with CD34 staining.

It is long recognised in epilepsy tumour series that a proportion of LEATs show a diffuse growth pattern, are low grade and lack the specific criteria for either ganglioglioma or DNT. These have been termed non-specific DNT⁸⁴, diffuse DNT⁸⁵⁻⁸⁷, low grade oligodendroglial tumours and recently a term PLNTY (polymorphous low grade glioneuronal tumour)⁸⁸ has been used over the decades to describe what are likely to be biologically the same tumours. These diffuse tumours predominate in the temporal lobe are MRI visible and intracortical and are composed of oligo-like cells but don't clearly show a glioneuronal element (for DNT) or dysmorphic neurones (as in Ganglioglioma). There is typically white matter rarefaction and they are CD34 positive (and IDH1 mutation- negative by definition). The WHO 2016 does not currently have a specific terminology for these tumours as yet⁷⁵; molecular characterisation aligns them more as a type of ganglioglioma than DNT (see section below).

Molecular studies in LEATS (DNT, ganglioglioma and diffuse LEATS)

Recent molecular subtyping of brain tumours has advanced tumour diagnostic approaches and is of relevance to overall prognosis and treatments⁸⁹. Although molecular biological understanding of the LEAT group lags behind more common gliomas, there is evidence of preferential involvement of the PI3K-AKT-mTOR and RAS-RAF-MAPK in preference to IDH1/ATRX/histone H3/TERT promotor mutations⁷⁴. Identification of common mutations to LEATS, as well providing diagnostic security, could indicate avenues for non-surgical medical treatments (e.g. BRAF inhibitors) for 'difficult to resect' cases as well as a potential influence on tumour epileptogenesis. From published studies to date there is evidence that BRAF V600E mutations predominate in ganglioglioma and FGFR1 mutations or duplications in the DNT group (found in up to 62% of tumours); these mutations appear to be mutually exclusive (see Figure 8).

BRAF V600E Mutation (LEAT Series)

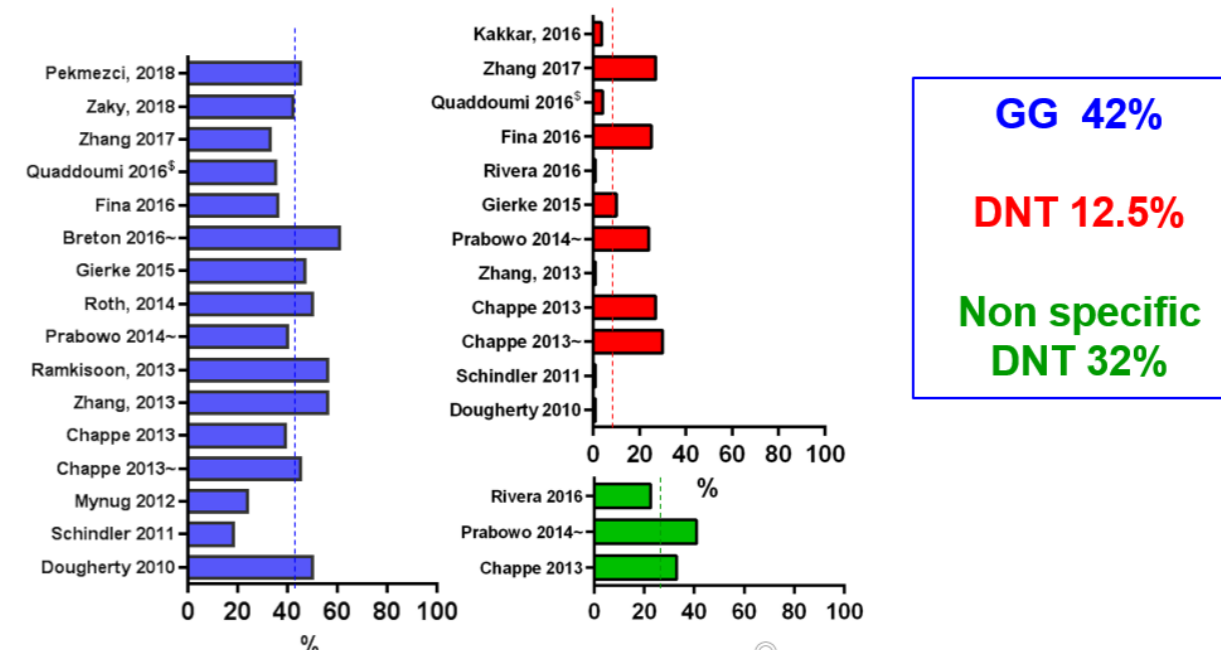


Figure 8: Comparison of studies of BRAF V600E mutations in ganglioglioma, typical DNT and non-specific or diffuse DNT types^{88,90,100}.

Furthermore, there is accumulating evidence that DNA methylation array analysis of these entities may provide a stringent classification in the future and their molecular grouping within the 'LEAT' histological spectrum^{97,101-103}.

Hamartomas in epilepsy surgery

The hypothalamic hamartoma has a strong association with intrinsic subcortical epileptogenesis and gelastic seizures and may be associated with the development of secondary cortical epileptogenesis and recently mutations in sonic hedgehog pathway have been identified¹⁰⁴. Unlike the tuberous sclerosis complex, hamartomas or malformative cortical lesions are relatively rarely reported in neurofibromatosis type 1 (NF1) a syndrome in which epilepsy occurs in up to 6% of patients. NF2 can be associated with multiple cortical glial-microhamartomas that are often incidental findings at post mortem. Interestingly, the presumed hamartomatous proliferation of meningioangiomas (MA), when associated with the NF2 complex, does not clinically manifest with seizures whereas in sporadic MA over 80% of patients present with epilepsy. The more common sporadic form of MA is typically solitary, and EEG suggests the epileptogenicity is confined to the adjacent cortex; seizures may persist in over half of patients following surgical treatment (see Figure 9).

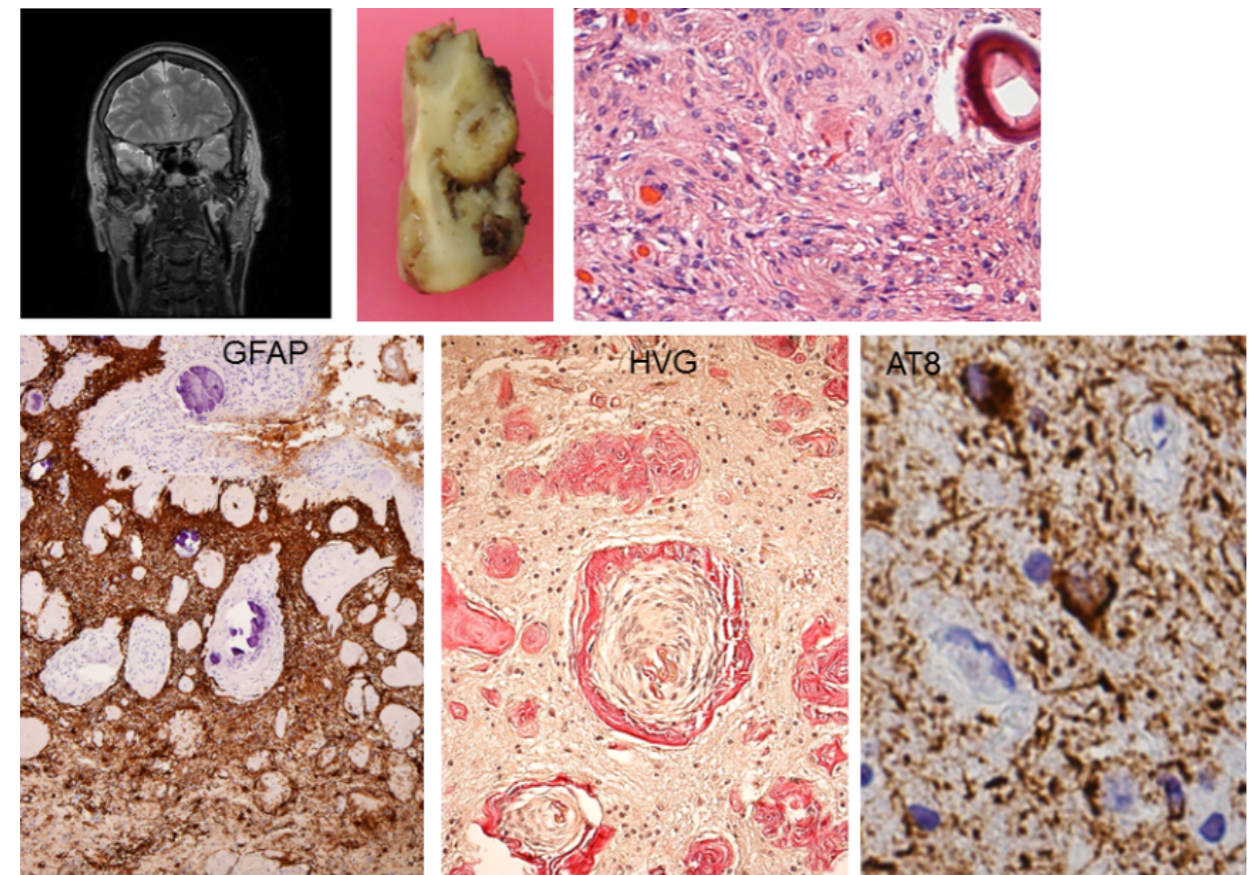


Figure 9. Meningioangiomas in the temporal lobe, sporadic in a patient age 60 with a long history of epilepsy, showing proliferation of meningothelial like cells around vessels on GFAP and HVG stain. Neurons in the region can show excess phosphorylate tau accumulation on AT8.

Vascular malformations in epilepsy surgery

Vascular malformations form up to 10% of lesions encountered in epilepsy surgical series and the main types are arteriovenous malformations (AVM) and cavernomas, with telangiectatic or angiodysgenetic lesions more rarely encountered. Although regarded as congenital, these lesions are dynamic and may even rarely arise *de novo*. Epilepsy is a common presenting clinical feature in 17% of AVM and is the most common presenting symptom in cavernomas (79%). Seizures may be generalised or partial. Common features to both AVM and cavernomas include extensive peri-lesional gliosis and tissue microhaemorrhages indicative of sub-clinical bleeds. The possible mechanisms inducing epilepsy include local ischaemia as result of arterio-venous shunting, the marked associated peripheral gliosis, haemosiderin deposition or secondary epileptogenesis occurring in the temporal lobe.

Cortical Malformations and Focal Cortical Dysplasias (FCD)

Table 3. ILAE 2011 classification of Focal Cortical Dysplasias

SUBTYPE	FCD TYPE I	FCD TYPE II	FCD TYPE III
DEFINITION	Isolated dysplasias that lack dysmorphic cells	Isolated dysplasias with dysmorphic cells	Combined dysplasias with other pathology
DEFINING CYTO-ARCHITECTURAL PATHOLOGY			
Subtype A	Abnormal radial cortical organisation	Dysmorphic neurons and abnormal lamination	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis.
Subtype B	Abnormal tangential cortical lamination	Dysmorphic neurons and balloon cells and abnormal lamination	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor
Subtype C	Abnormal radial organisation and tangential cortical lamination	-	Cortical lamination abnormalities adjacent to vascular malformation
Subtype D	-	-	Cortical lamination abnormalities adjacent to other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis

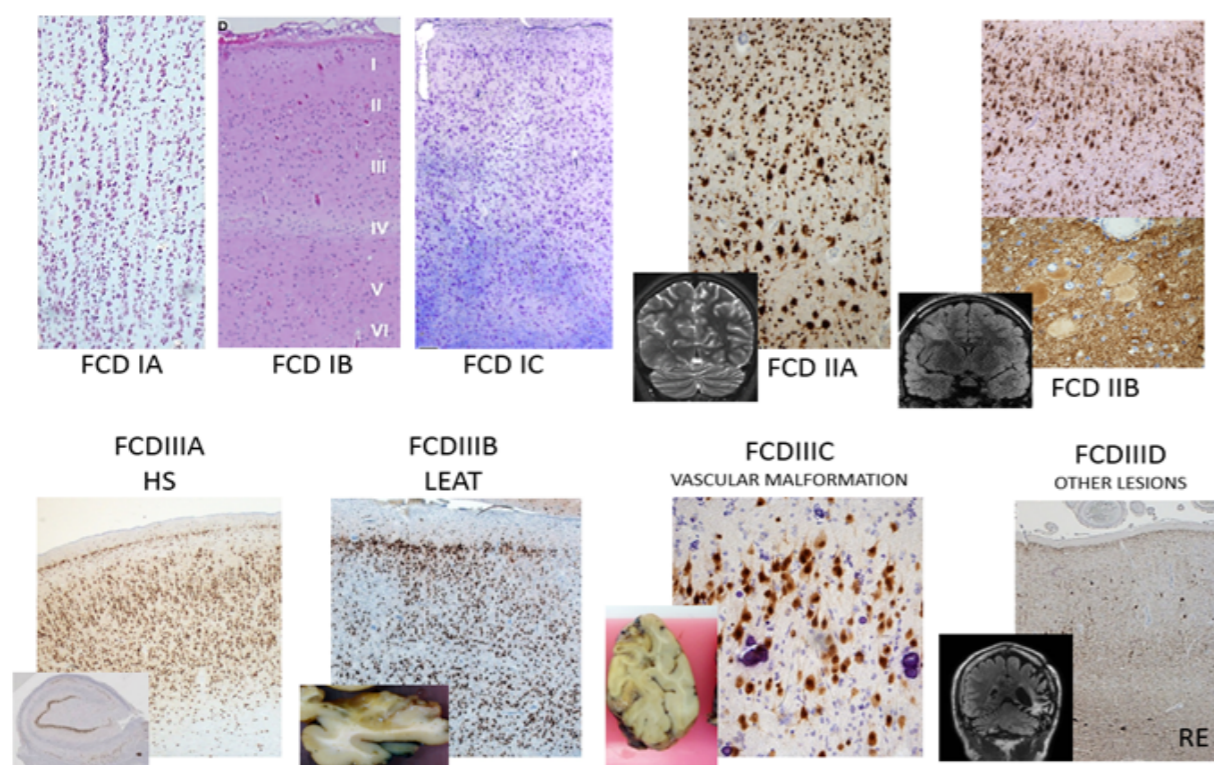


Figure 10. Illustrating the 9 main subtypes of FCD in the ILAE scheme (RE = Rasmussen's encephalitis). The pathology is detailed in text below.

Focal Cortical Dysplasias (See Table 3, Figure 10 and 11)

The focal cortical dysplasias (FCD) represent a spectrum of localised brain abnormalities of the cortical cytoarchitecture and myelo-architecture, considered to represent malformations of cortical development. They are highly associated with epilepsy. The original description of FCD was by Taylor *et al*¹⁰⁵ for a specific cortical abnormality bearing 'balloon cells'. In the following decades, with increased availability neuroimaging and surgical treatments for focal epilepsies, the term 'focal dysplasia' became generically used for varied malformations, from heterotopia and polymicrogyria to subtler microscopic 'microdysgenesis' of the cortex. Additional terms were introduced as 'mild dysplasia', 'non-Taylor dysplasia', 'cyto-architectural dysplasia', 'glio-neuronal hamartia' and several pathology-based classifications systems were proposed to unify terminology¹⁰⁶⁻¹⁰⁸.

The ILAE classification of FCD in 2011¹⁰⁹ is the current scheme and can be consistently applied between pathologists¹¹⁰ and has shown to be of clinical diagnostic and prognostic utility (see Table 3). Some key features were the segregation of isolated dysplasia from dysplasias associated with other lesions. Microscopic malformations lacking cortical laminar abnormalities (previously termed microdysgenesis) remained separated from FCDs under the umbrella term of 'mild malformations of cortical development' (mild MCD) (see section below).

FCD is the commonest malformation in large epilepsy surgical series¹¹¹. It represents the third most common lesion in adult epilepsy surgical series (20% of diagnoses; hippocampal sclerosis and tumours being more common) but the commonest abnormality in paediatric epilepsy series (40-50% of diagnoses)^{2,3,112,113}.

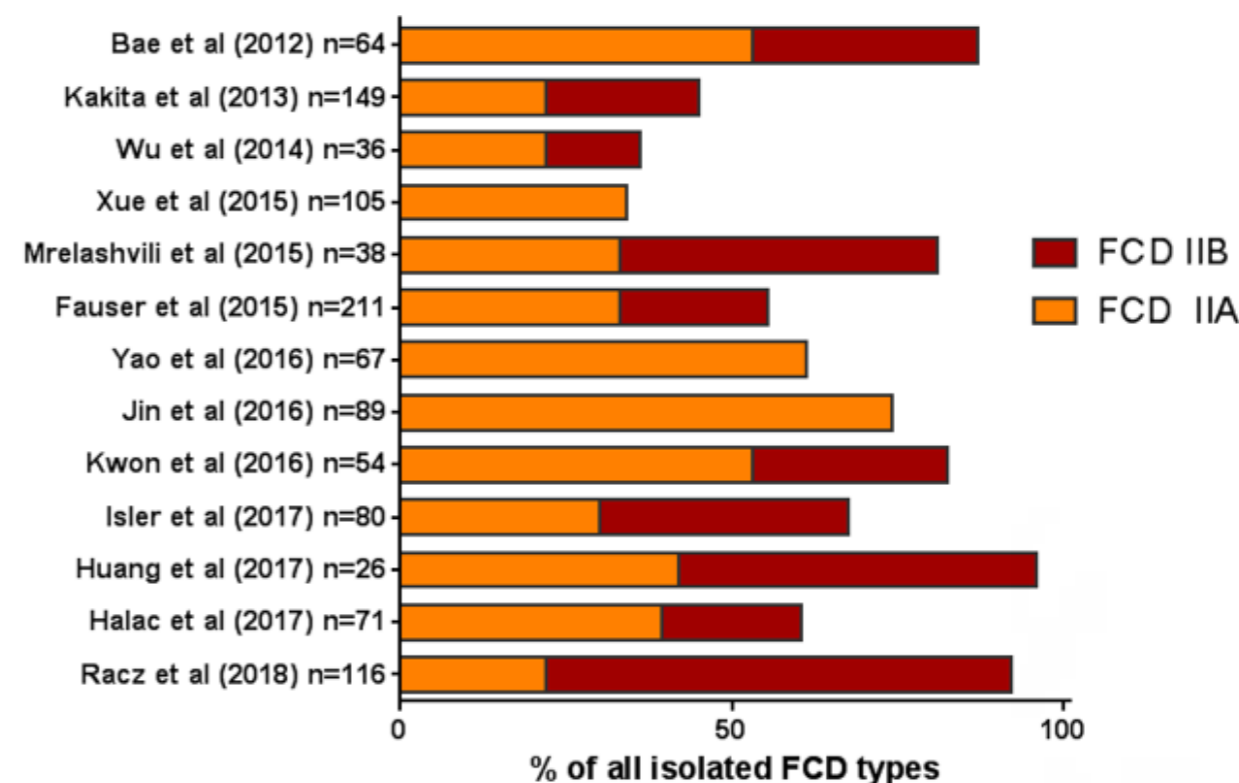


Figure 11 (see above bar chart): Relative incidence of FCD type IIA and IIB in reported series of isolated FCD in epilepsy series since the ILAE 2011 classification (2012-2018). Overall FCDIIA accounts for 29.8% and FCDIIB for 35.2% of all resections.

The relative incidence of FCD subtypes varies¹¹⁴ but based on larger surgical series of isolated FCD, FCD IA represents 46%, FCD IB 19%, FCD IIA 15% and FCD IIB 39%^{2,113,115-120}. The incidence of FCD IIIA varies between 11% to 46% in temporal lobe epilepsy series^{9,72,121} and the reporting of FCD IIIB is even more variable⁷⁶ with no specific data available for FCD IIIC and IIID. Seizures associated with isolated FCD usually begin in the first decade of life, often present in infancy, but can present in adolescence or even adulthood. There is no clear sex predilection or geographical clustering.

MTOR pathway and FCD

A long-held theory was that FCD was a genetic condition and a forme-fruste of TS due to histological similarities. Recently, significant genetic advances have been made through the identification of mutations in mTOR pathway genes in FCD¹²²; for recent review see [123]. FCD type II shares histologically features with the more extensive, conditions of both hemimegalencephaly (HME) and tuberous sclerosis (TS). Mutations of *TSC1* and *TSC2* occur in TS and *AKT3*, *DEPDC5*, *MTOR*, *PIK3CA* or *PTEN* in HME¹²⁴⁻¹²⁷, which involve the phosphatidylinositol 3-kinase (PI3K)/AKT3/target of rapamycin mTOR signalling pathway. FCD is mainly sporadic but some familial cases of FCD II are reported¹²⁸⁻¹³⁰. There was histological evidence for activation of the mTOR pathway in the dysmorphic neurones and balloon cells of FCD II^{131,132}. Intrauterine human papilloma virus was identified as a potential causative pathogen in FCDIIB and activator of mTOR¹³³ but not confirmed in subsequent studies^{134,135}. Recently, deep sequencing studies have identified somatic activating mutations in MTOR and DEPDC5/ GATOR complex, mainly in type II FCD. It seems likely that as yet unidentified somatic, as well as germline mutations in mTOR pathway genes, may be involved in the pathogenesis of majority of FCD¹³⁶ and that FCD, TS and HME represent a disease continuum^{122,127}

of brain ‘overgrowth’ disorders^{126-129, 136-142}. The phenotypic variation associated with same somatic mutation could be dependent on the timing of the acquisition of the mutation during development in the post-zygotic embryo, influencing level of tissue mosaicism and extent of malformation and its clinical influence¹⁴³. Furthermore, in FCD cases with multiple tissue samples, alternate allele fractions of MTOR mutations have been shown with an epicentre (highest allele fractions) corresponding to the most epileptogenic region¹³⁷. MTOR mutations are activating and GATOR complex/ DEPDC5 mutations, inactivating. Identification of somatic and germline mutations reported in DEPDC5 in some cases also support a ‘2 hit’ model¹²⁸. NPRL2 and NPRL3 mutations have also been identified in cases of FCD Ia¹⁴⁴. FCD can also co-exist with other common epilepsy gene mutations as *SCN1A* gene which may represent other susceptibility factors¹⁴⁵. Finally, of importance germline mutations of MTOR have been shown in patients with focal and generalised epilepsy with no lesions on MRI¹³⁸.

Risk factors and pathogenesis for other FCDs

Specific risk factors for FCD III, above those for the main associated lesion, remain to be fully validated; for example more febrile seizures were noted in HS cases with FCDIIIA compared to without⁷² and higher seizure-frequency and male predominance in FCDIIIB compared to tumours without FCD IIIb¹⁴⁶.

Macroscopic features of FCD

Tissue resections FCD II may appear normal to the naked eye but in some cases broadening of the cortex with poor demarcation from the underlying white matter is perceived and the tissue may appear firmer. The size of the abnormality varies, typically being a few centimetres across involving adjacent gyri, but can be localised to the depth of one sulcus, more extensive through one hemisphere or multifocal. In FCDIII the main lesion itself may be more apparent at the macroscopic level e.g. the tumour or cavernoma.

Microscopic features

FCD type I Abnormal cortical architecture defines this pathology. Three subtypes are recognised (Table 3); In FCD IA an exaggerated radial or ‘microcolumnar’ cortex is observed with rows of small neurones arranged perpendicularly in the cortex¹⁴⁷, often more apparent in mid-layers (Figure 12). In FCDIB the normal six-layered cortical architecture appropriate for anatomical site, is lacking (dyslaminar); this may involve all layers (a-laminar cortex) or specific layers¹⁰⁹. FCDIC has the combined features of FCD IA and B. FCD I may be accompanied by blurring of the grey-white matter boundary, occasional hypertrophic or immature neurones as well as increased numbers of single, ectopic white matter neurones in the underlying white matter¹¹⁷. There is no diagnostic immunohistochemistry biomarker for FCDI; NeuN is helpful in assessment of cortical architecture, a relative lack of mTOR pathway activation has been noted and abnormal expression of development markers has been described including SOX2, Otx1, DCX and Map1b^{148,149}.

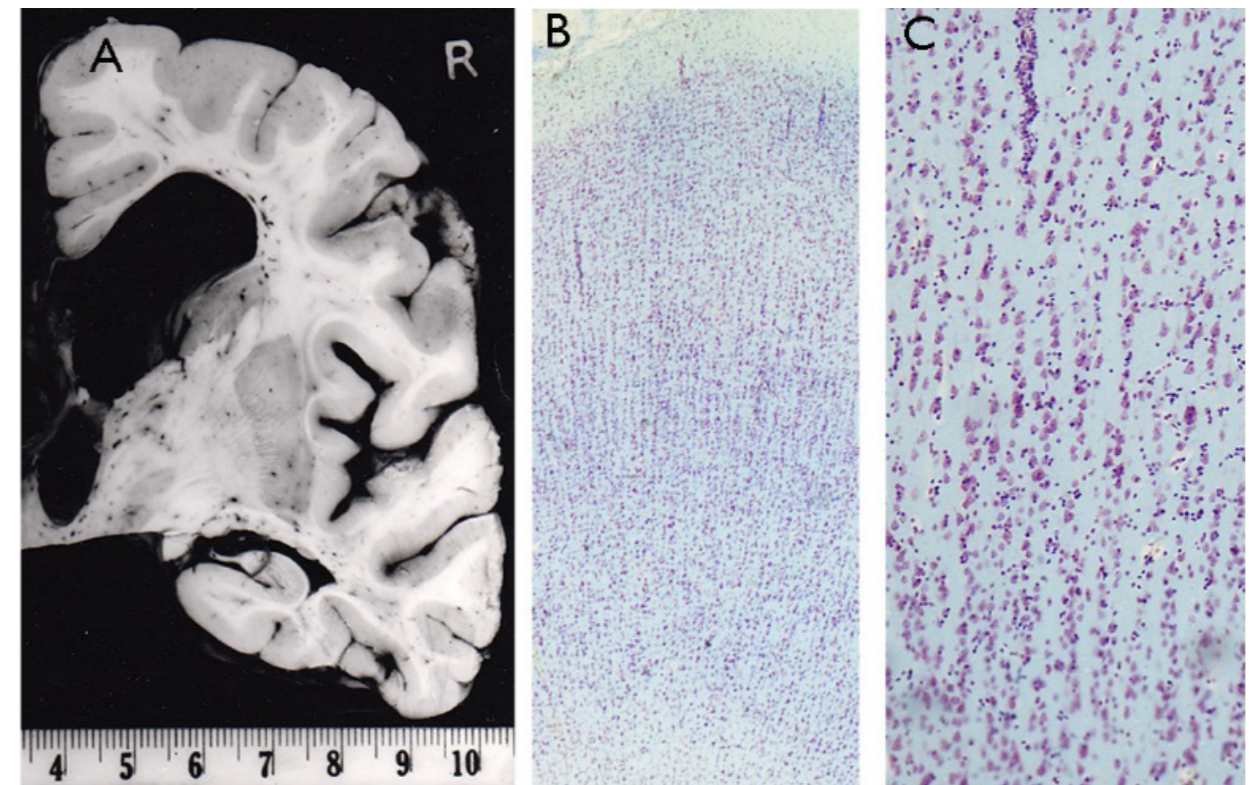


Figure 12 - FCD Ia. Post mortem case from a patient with childhood onset epilepsy and in many regions of the cortex (normal to the naked eye) radial alignment of neurones was present (shown in cresyl violet).

FCD type II (see Figure 13): The hallmarks are the presence of abnormal neuroglial cell types in addition to disorganisation of the cortical architecture¹⁰⁹. Hypertrophic pyramidal neurones and abnormal neurones with irregular, globoid shapes, orientation and dendritic patterns (**dysmorphic neurones**) populate the full thickness of the cortex and subcortical zone or are scattered through laminae with intervening normal neurones; more rarely they can predominate in one laminae¹⁵⁰. Nissl staining of dysmorphic neurones is coarse with elliptical “thickening” of the nuclear membrane^{105,108}. The normal six-layered horizontal lamination of the cortex in these regions is lost as well as radial organisation, when compared to adjacent normal cortex. The normal myeloarchitecture of the cortex is also typically disrupted in FCD II and the white matter is hypomyelinated¹⁵¹, but more often in FCD IIB than IIA. Cortical layer I typically remains hypocellular and distinct from deeper laminae. **Balloon cells** if present define the lesion as type FCD IIB. These enlarged, round cells with glassy-pink cytoplasm and eccentric, often multiple nuclei on H&E, are typically located in the superficial layers as well as the subcortical regions around vessels and in regions of hypomyelination, trailing in the white matter towards the ventricle^{105,108}.

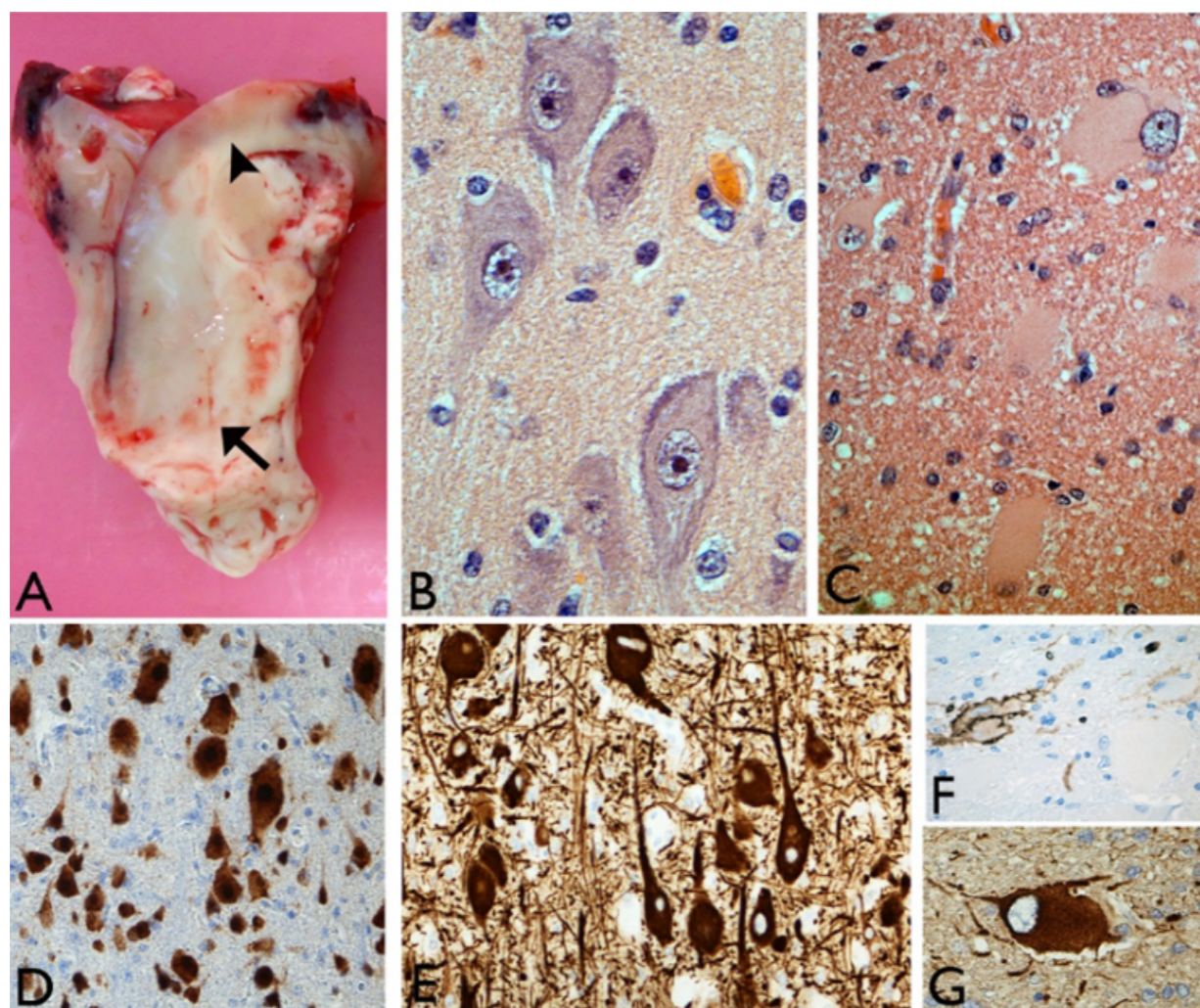


Figure 13 - FCD IIB: A. Macroscopic features in fresh resected tissue show region of cortical thickening (arrow in depth of sulcus) compared to more normal marginal cortex. B. Dysmorphic neurones are present in the cortex on H&E stain. C Balloon cells predominate on the white matter. Immunohistochemistry for D. NeuN and E. Neurofilament can highlight the dysmorphic neuronal component and F. CD34 and G. nestin can highlight the balloon cells.

The pathology can be diagnosed on conventional stains, but immunohistochemistry is helpful for confirmation of FCD II in small biopsies or where representation of abnormal cell types is limited. NeuN and neurofilament antibodies can aid in the identification of dysmorphic neurones and abnormal lamination whereas balloon cells are highlighted with intermediate filament antibodies (vimentin> GFAP-delta>nestin>GFAP)¹⁵². Retained abnormal expression of immature or developmental regulated proteins including CD34, DCX, β 1-integrin among others^{148,149,153-155} has been shown in FCD II as well as upregulation of proteins of potential relevance to epileptogenicity, including mTOR pathway activation markers, connexins and inflammatory mediators¹⁵⁶⁻¹⁵⁸. The overall density of cortical neurones in FCD IIB is reduced compared to controls¹⁵⁹. Layer specific cortical markers have been used to highlight disturbance to the normal cortical layer patterning¹⁵⁹ and abnormal migratory events. Dysmorphic neurones mainly represent cortical projection neurones immunophenotypically (Muhblener 2016) and abnormal distribution of inhibitory interneurons (Parvalbumin) within the FCD IIB cortex has also been shown.

FCD type III

The ILAE classification of FCD introduced type III (dysplasias adjacent to epileptogenic lesions) in order to separate this group from isolated FCD type I¹⁰⁹.

In type IIIA the temporal neocortex adjacent to hippocampal sclerosis can show FCD I-like dyslaminar abnormalities, small 'lentiform' neuronal heterotopias, or a more specific cortical abnormality also termed 'temporal lobe sclerosis'⁷², characterised by clustering of neurones in cortical layer II accompanied by neuronal loss and gliosis in the superficial cortex (Figure 14).

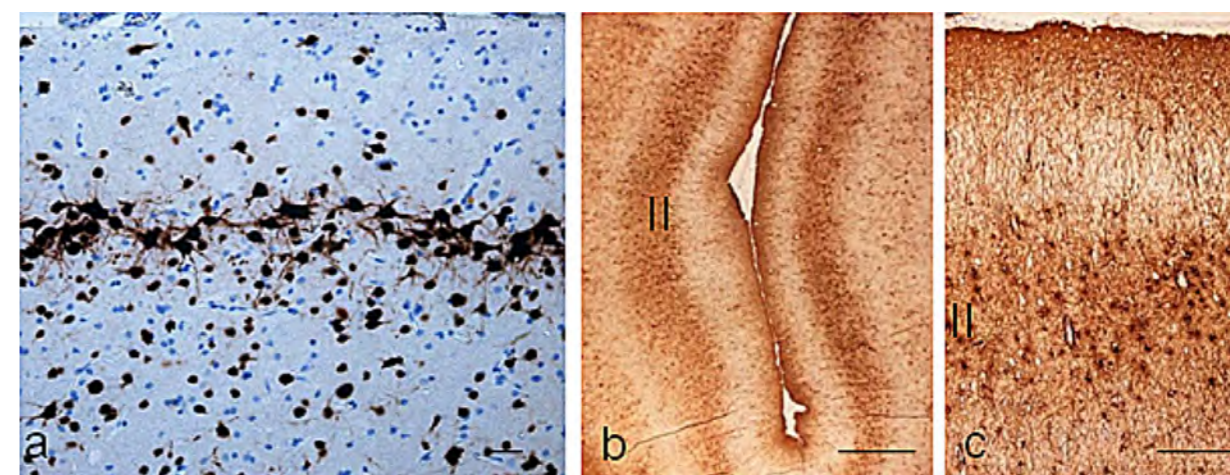


Figure 14: FCD IIIa. A NeuN staining showing abnormal aggregation of neurones in layer II. This is virtually always accompanied by gliosis in the superficial cortex which is laminar involving layer II/III corresponding to laminar loss of neurones / temporal lobe sclerosis.

In FCD IIIB (dysplasias adjacent to low grade epilepsy-associated tumours (LEAT)) FCD I-like dyslaminar abnormalities and hypertrophic neurones have been variably described^{76,109} and more commonly reported adjacent to gangliogliomas and dysembryoplastic neuroepithelial tumours (DNT)¹⁴⁶. However, there is marked variation in the reporting of FCD IIIB (see Figure 15) and the main differential is distinguishing a true dysplasia from the cortical infiltration zone of the tumour.

FCD IIIC is cortical dyslamination or abnormal cytoarchitectural composition (hypertrophic neurones) adjacent to vascular malformations as cavernomas, meningioangiomas etc.

FCDIIID encompasses the spectrum of alterations of the cortical architecture (cortical dyslamination, hypoplasia) and myeloarchitecture reported adjacent to other perinatally acquired lesions or injuries, including infarcts, traumatic and inflammatory lesions as Rasmussen's encephalitis.

The pathogenesis of FCD III is considered to be different from isolated FCD, being acquired rather than primarily genetic and arising at later developmental stages affecting post-natal cortical maturation, regeneration and reorganisation. Its aetiology is linked with that of the associated main pathology and factors as prematurity, hypoxic-ischaemic insult, febrile seizures, head trauma, infection are potential pathogenetic causes for types IIIA and D¹⁶⁰. The micro-columnar patterns in some FCD I and III may represent arrested maturation with persistence of developmental, vertically arranged pyramidal cells and their bundled projections of axons and dendrites¹⁶¹⁻¹⁶³. In FCD IIIB a pre-existing cortical dysplasia on which the tumour arises still remains an unproven hypothesis.

Incidence of FCD IIIB in epilepsy tumour series

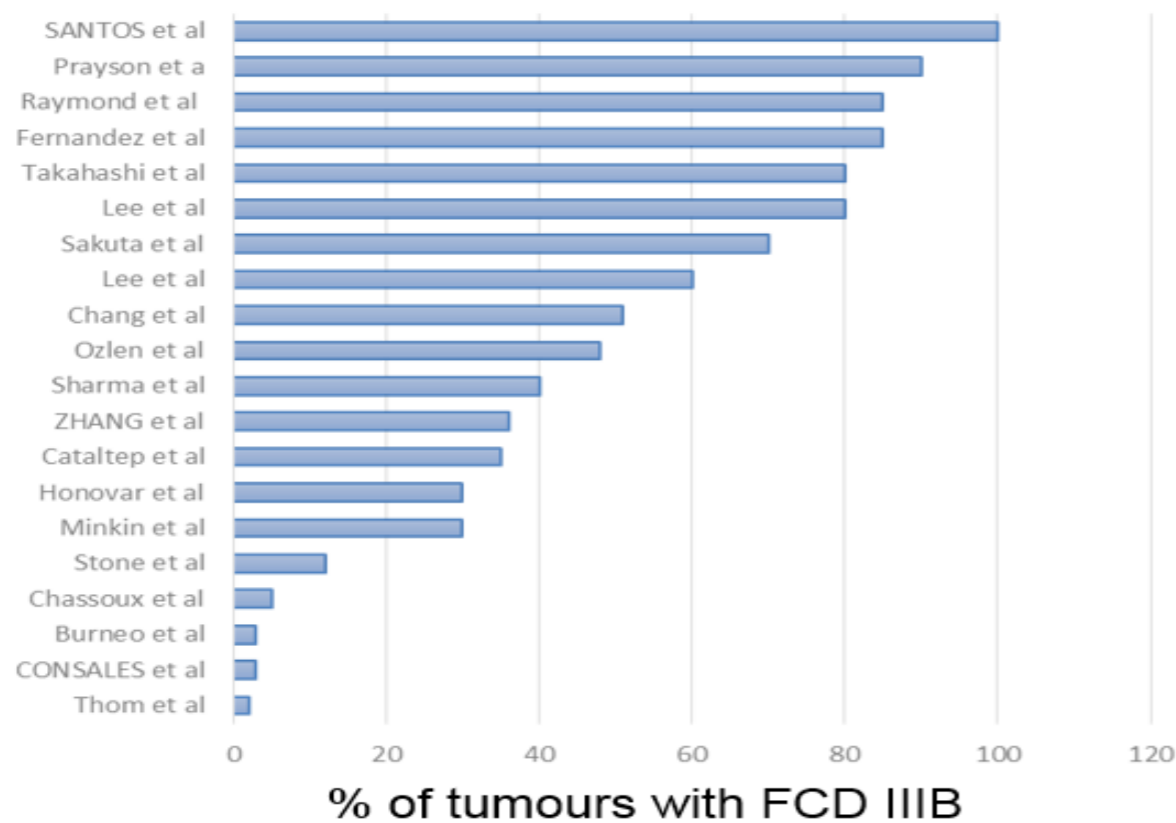


Figure 15. Variability of reporting associated FCD type IIIb with DNT (from 0 to 100% of cases) in reported series from 1994 to 2017. Variation likely relates to lack of well-defined criteria for FCD IIIb and over-interpretation of tumour infiltration region as dysplasia. Peritumoural pathology nevertheless is likely to be relevant to epileptogenicity, completeness of tumour removal and long-term seizure outcomes.

Surgical treatments and outcome

A recent meta-analysis of 1190 operated cases with FCD/MCD of all types showed 56% achieved a good outcome following surgery¹⁶⁴. Studies of operated FCDIIB report seizure free outcomes as high as 75%¹¹³ and 87.5%¹¹⁸. There is evidence for better outcomes post-surgery for FCD IIB than FCD I and III¹⁶⁵. Post-surgical outcome in terms of seizure control is likely to be influenced by many factors including the dysplasia type, the extent or completeness of resection (of the epileptogenic zone or radiological lesion), the presence of a second pathology (as hippocampal sclerosis) and the length of follow up. Completeness of excision (as assessed by post-operative MRI or histological margins) is associated with a better outcome^{118,166-168} with excision of the cortical component more critical than the white matter¹⁶⁹. Clinical improvements have been reported for MRI-negative FCD¹⁷⁰ and equally good outcomes for surgery carried out in adulthood and childhood¹⁶⁶.

The relative contribution of FCD III versus the main lesion, to epileptogenicity and outcome following resection still remains to be clarified^{121,146}. There are studies that report worse outcome in HS patients with FCD IIIA compared to those without^{9,121} better outcomes¹⁷¹ and no significant differences^{72,172}. In a recent study of tumour-associated FCDIIB, the clinical outcome was not significantly different from that of isolated tumours without dysplasia¹⁴⁶.

Mild Malformations of cortical development

Mild MCD are more often reported in the lateral temporal lobe in association with HS¹⁷³ but also as a more widespread cortical alteration¹⁷⁴. Histopathology features include excess of heterotopic and other neurons in layer I, including Cajal-Retzius cells (mild MCD type I) although precise pathological criteria for this remain poorly defined¹⁰⁹. Mild MCD type II encompasses an excess of single or clusters of neurons of normal morphology in the white matter, deep to the immediate subcortical region. This needs to be distinguished from normal interstitial white matter neurones. In temporal lobe epilepsy specimens, quantitative evidence of increased numbers of white matter neurones in otherwise apparently normal appearing white matter has been reported since the 1980s¹⁷³. Initially termed microdysgenesis, this observation had been confirmed by several subsequent studies¹⁷⁵⁻¹⁷⁹. A recent study highlighted the potential of whole slide scanning and automated image analysis methodology to the analysis of type II Mild MCD¹⁸⁰; In this study of 142 TLE cases with normal white matter, this method was shown to be as accurate as stereological methods with the added advantages of time-efficient unbiased, analysis of the entire white matter (Figure 2a). It is likely that such applications will become more available in the era of digital pathology and when calibrated against 'in-house' normal control values, clear definitions for Mild MCDII can then be applied. This will enable future correlation with neuroimaging and clinical outcomes in larger patient datasets. In a single case based on NeuN or MAP2 staining, densities of > 8 neurones per high power field (or >100 neurones /mm²) represent definite mild MCD II [180] and >30 neurones/mm² possible mild MCD II^{109,180}.

The significance of mild MCD variants in terms of independent epileptogenicity is unclear¹⁰⁹ but there is some evidence for better seizure-free outcomes when this pathology is present¹⁸⁰. The cause of increased white matter neurones in epilepsy remains unexplained. Proposed theories include a reduction in the normal rate of elimination of subplate neurones during maturation or a true 'heterotopia' with arrested migration of neurones destined for the cortical plate. Elucidation of events may come through study of the proportional representation of different neuronal phenotypes and their maturation for example using Tbr1, a marker of immature subplate neurones, as recently shown¹⁸¹.

Oligodendroglial hyperplasia/oligodendrogliosis (see Figure 16)

The presence of increased numbers of oligodendroglia cells, particularly in the subcortical region in patients with epilepsy undergoing surgical resection has been long recognised. Whether this is epiphenomena of seizures or is a primary/developmental process is unclear. Specific oligodendroglial cell populations can be highlighted with Olig2 to distinguish them from other glial cell types and quantified. Schurr *et al*¹⁸² describe this histological feature in a recent series of cases from frontal lobe surgical resections. In 22/52 otherwise non-lesional cases they noted an increase in Olig2 - positive cells in the deep cortex and white matter and MRI abnormalities were also noted. They suggest this represents part of the spectrum of mild malformations of cortical development. Increased olig2 cells was also reported in the white matter and grey/white matter junction were observed in paediatric pathologies and in patients undergoing multilobar resections and correlated with non-focal seizures; a role for these cells in abnormal interconnections was speculated on [183]. Impaired oligodendrogliosis has also been associated with myelin pathology in focal epilepsy¹⁸⁴.

Concepts of Epileptogenesis in focal pathologies

The term *epileptogenesis* encompasses the cascade of cellular events, following which a brain develops spontaneous seizures or epilepsy. Epileptogenesis is often divided into three stages: the acute event (the triggering insult or initial seizure), a latent period (clinically silent), and spontaneous seizures. In humans, the latent period can last for months or years. The main challenges in studying the processes of epileptogenesis in advanced-stage human tissues is to distinguish underlying

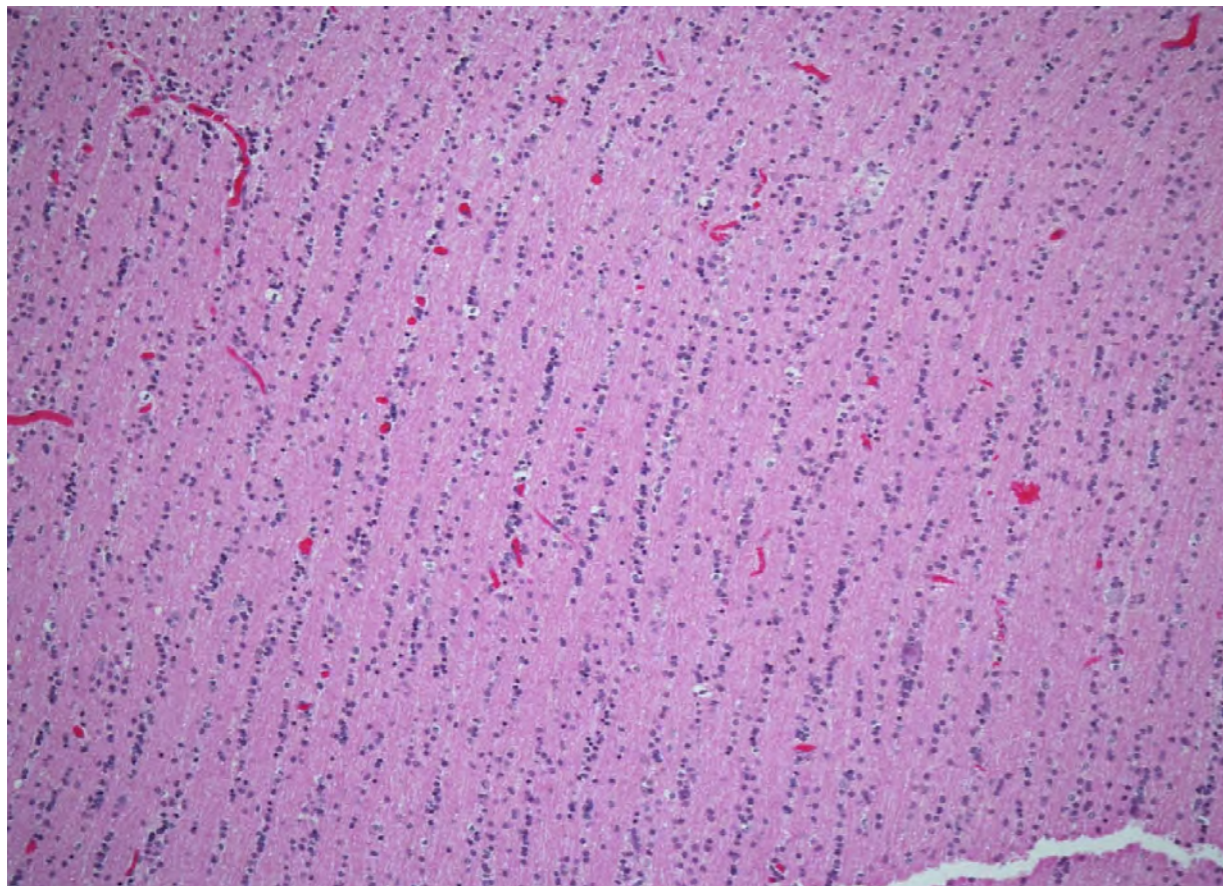


Figure 16. Prominence of oligodendroglial cells in the temporal lobe white matter, can be striking in some cases.

pre-existing abnormalities from secondary maladaptive reorganisational changes. It is also likely that multiple epileptogenic mechanisms operate in concert. Understanding epileptogenesis is essential to identifying new therapeutic targets. At present, most available drugs are 'anti-epilepsy' rather than 'anti-epileptogenesis', but there are promising new options, modifying cellular responses that could prevent epilepsy in the first instance. Important areas include targeting inflammatory responses in epilepsy, blood brain barrier dysfunction, astrocyte and neuronal generation and degeneration that could promote establishment of seizure networks. For example, in tumour-associated epilepsy likely mechanisms promoting seizures include, peritumoural changes, including altered pH, neurotransmitter levels, inflammation, haemosiderin deposition, abnormal networks, gliosis, altered gap junctions and blood brain barrier dysfunction

Inflammation

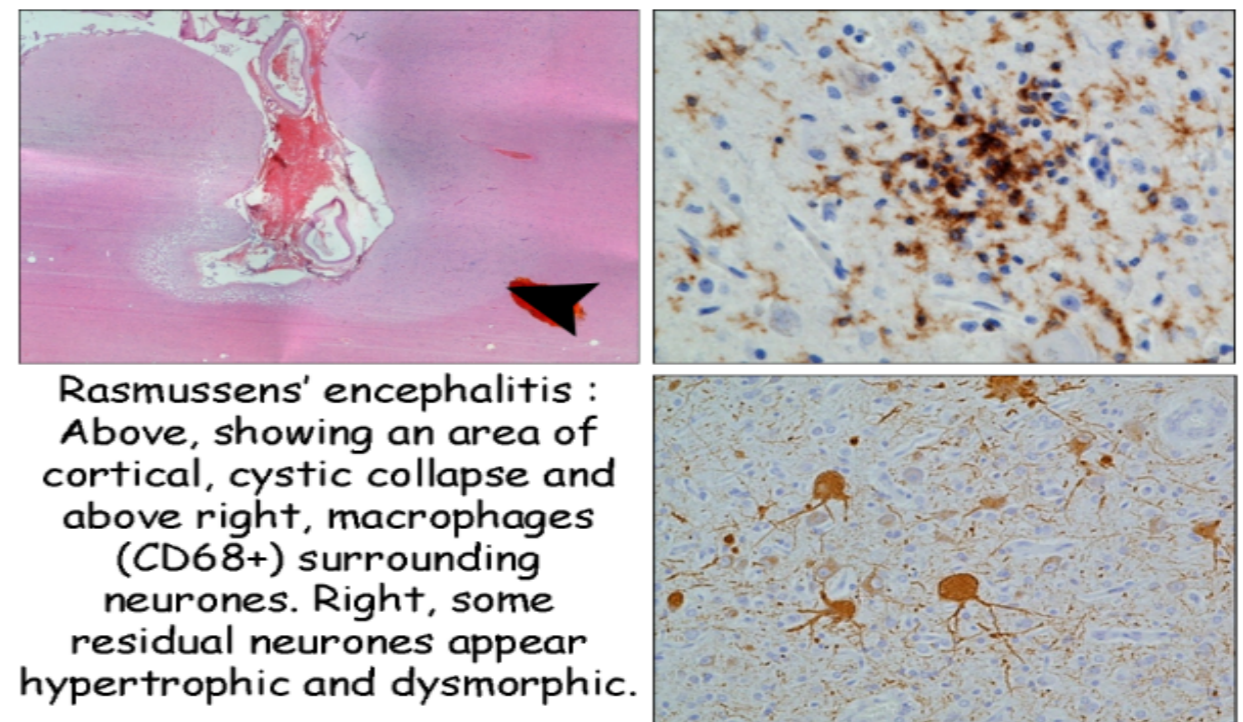
There is accumulating evidence for activation of inflammatory pathways in focal acquired epileptogenic lesions and an exponential increase in the number of publications on this topic¹⁸⁵. A vicious cycle of an initial trigger (abnormal neuronal activity) stimulating innate or adaptive immunity and neuroinflammation which triggers seizures and further neuronal death promoting an inflammatory response that can arise and different glial cells types (microglia, astroglia) recruited into the process¹⁸⁶. A recent meta-analysis of 66 published articles¹⁸⁷ summarised that on 1934 patients, 51 inflammatory mediators in serum, CSF or brain tissue had been studied, with IL-1RA, IL-1, IL-6, IL-10, IFN- and TNF-α the commonest studied. They concluded that inflammatory pathways

are involved in epilepsy and that future studies for targeted anti-inflammatory treatment could be of benefit.

For example, the activation of inflammatory pathways has been explored in hippocampal sclerosis pathogenesis, looking for evidence of upregulation of inflammatory cytokines and chemokines; the IL-1 family has been most studied with evidence of increase in IL-1α regardless of presence of HS or not whereas increase in IL-1β expression is seen particularly with HS and chemokines CCL3 CCL4 and CCL5 show higher expression in TLE neurones than controls (see reference for recent review [188]).

Autoimmune encephalitis

Patients with antibodies to intracellular or surface antigens can present with acute onset of epilepsy, psychiatric illness, cognitive decline and underlying limbic encephalitis (e.g. GAD, LGI1)^{189,190}. Rasmussen's encephalitis (RE) is a rare sporadic syndrome of presumed autoimmune aetiology typically presenting in childhood with intractable seizures and associated with progressive unilateral hemispheric atrophy and neurological deficit¹⁹¹. The severity of the inflammatory process and the extent of the cortical scarring vary with the duration of the disease process and traditionally has been divided into four stages. The early stages (1 and 2) are characterised by more active chronic inflammation and later stages (3 and 4) with less active inflammation and more extensive scarring. Inflammatory infiltrates in the cortex consist mainly of T lymphocytes (CD8>CD4+) with perivascular and perineuronal clusters. B lymphocytes are less frequently present in the perivascular cuffs and plasma cells are rare. Widespread activation of microglia may be seen as well as microglial clusters and nodules (see Figure 17), but macrophage infiltrates are less common. Patchy neuronal degeneration, neuronophagia and neuronal dropout are present in the early stages.



Rasmussens' encephalitis :
Above, showing an area of cortical, cystic collapse and above right, macrophages (CD68+) surrounding neurones. Right, some residual neurones appear hypertrophic and dysmorphic.

Figure 17 - Rasmussens' encephalitis, see above.

With progressive damage, neuronal ballooning with distortion of cell shape, neurofilament accumulation, and laminar disorganisation may also be noted, reminiscent of cortical dysplasia (FCD IIIc) and apoptotic neurones have been identified^{189,191}. In the later stages, large areas of pan-laminar or patchy cortical necrosis are characteristic with extensive neuronal loss, astrocytic gliosis and cortical spongiosis and the inflammatory process is less prominent. Cortical scars may be extensive, involving a whole gyrus or more 'punched out' wedge-like areas of destruction may be observed. The topography of the inflammatory process varies within specimens with regions of either atrophy, active inflammation alternating with stretches of uninvolved cortex. The multifocal nature of the disease process highlights why cortical biopsies may give a false negative result. Patchy inflammation and myelin loss in the underlying white matter and involvement of the deep grey nuclei may also be present in RE and inflammation may extend to the hippocampus and additional hippocampal sclerosis may be present. In cases where post mortem tissue is available, true bilateral disease with associated inflammatory change is probably very rare.

Post Mortems in Epilepsy Related Deaths and Sudep

Neuropathology approaches

Neuropathological investigations are mainly directed to the following questions: (i) Identification of structural lesions or cellular alterations that caused seizures (epileptogenic focus), (ii) the secondary effects of seizures on the brain and (iii) if epilepsy was directly related to the cause of death (Epilepsy related deaths (ERD)). The latter can include an accident during a seizure, status epilepticus or sudden and unexpected death in epilepsy (SUDEP) (Table 1). SUDEP is defined as *"Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where autopsy examination does not reveal a toxicological or anatomical cause of death."*¹⁹². The main categories of cause of death are listed opposite in Table 4.

SUDEP is the commonest cause of premature death in adults with epilepsy and is more common in patients with poorly controlled generalised convulsive seizures¹⁹³. They are typically unwitnessed deaths, often nocturnal or occurring during sleep and, by definition, no cause of death is ascertained at post-mortem¹⁹⁴. The mechanisms causing SUDEP are unknown but current evidence, including from witnessed SUDEP deaths in patients undergoing investigations on epilepsy monitoring units¹⁹⁵, favour a centrally mediated depression of cardiac and respiratory regulation. SUDEP affects all ages but peaks in young adults¹⁹⁴ and the incidence is estimated around 1 to 1.2 per 1000 per year in people with epilepsy amounting to 500 deaths per year in the UK alone.

In suspected ERD and SUDEP cases, a 'complete' post-mortem examination includes external and full internal examination, and toxicology, including anticonvulsant levels^{196,197}. The brain should be examined by a neuropathologist, or personnel with sufficient neuropathology training. Epilepsy-related and sudden deaths typically fall under the remit of the Coroner. Some of the practical problems include that full clinical information regarding the epilepsy history, including investigations carried out during life, may not be available at the time of the post mortem. Also, in unwitnessed SUDEP there may be long post-mortem interval, particularly if the deceased was living alone or death unwitnessed. Brain retention protocols and coronial practice varies widely regarding what is permissible regarding epilepsy-related death investigations, which may restrict the pathologist's examination. The Royal College of pathologist's guidance document recommends that retention of the brain with examination after a period of fixation is advisable to enable optimum neuropathological examination. It further specifies a regional block sampling protocol (any lesion or abnormality detected, the hippocampus, amygdala, basal ganglia with insular cortex, watershed frontal cortex, thalamus brainstem and cerebellum), taken from both hemispheres as

epilepsy pathology can lateralise. The rationale of this approach is that through a systematic and histological examination, an underlying unsuspected cause of death, for example vascular disease, inflammation, infection (meningoencephalitis) or metabolic disorder (e.g. mitochondrial disease), is excluded thus enabling more stringent SUDEP classification. Samples for toxicology are mandatory in sudden ERD investigations, whereas other investigations (microbiology, virology, metabolic tests, genetics etc.) tend to be tailored for a particular case, directed by circumstances of death, clinical data and post-mortem findings.

Table 4. Main cause of epilepsy related deaths.

Category		Comments
Epilepsy-related deaths	Status Epilepticus	Clinical or EEG evidence of unremitting convulsive or partial seizures (or EEG evidence of seizure activity in non-convulsive status) for > 30 mins period prior to death.
	Aspiration during a seizure	Confirmation by histology required in distal airways. Gastric contents may be displaced in main airways (trachea and bronchi) in sudden death without true aspiration
	Accidental death	PM examination carried out to confirm e.g. drowning, trauma occurring during a seizure including head injury.
	Suicide	Patients with epilepsy have increased incidence of neuropsychiatric disease, depression
	As a result of surgical or medical treatment of epilepsy	Drug reaction/interaction/accidental overdose Post-surgical complication (rare)
	SUDEP - Definite	Sudden death in patient with known epilepsy diagnosis (excluding status epilepticus) Negative histology, neuropathology and toxicology is required. The cause of epilepsy may be identified.
	SUDEP - Possible	As above but competing cause of death identified at PM (e.g. cardiac hypertrophy).
SUDEP - Probable	As above but the PM examination was incomplete (e.g. no neuropathology).	
SUDEP - Near miss	As above but the patient is resuscitated and survived for a short period without regaining consciousness. In these cases, more global hypoxic-ischaemic brain damage can be seen.	
Death from the underlying condition causing epilepsy	e.g. Alzheimer's disease, Glioblastoma, Stroke etc.	PM examination of the brain to confirm underlying pathology and any potential contribution to the mode of death (e.g. brain swelling or intra-tumoural haemorrhage)
Cause of death is unrelated to epilepsy		Other cause of death identified. Epilepsy may be included in part II of the certificate if indirectly contributing.

Neuropathology findings reported in SUDEP (see Figure 18 opposite):

It is important to bear in mind that in a SUDEP post mortem the brain is not always normal even though, by definition, there is no neuropathological explanation for cause of death. The brain external surfaces and coverings should be examined in a systematic way, being careful to assess for any features associated with brain swelling as uncal and tonsillar herniation. Mild degrees of brain swelling with effacement or fullness of the gyri are a not uncommon features in SUDEP¹⁹⁸, due to mild degrees of acute cerebral oedema, but alone are insufficient for a cause of death. The external surface of brain in epilepsy can also reveal old contusions, evidence of previous surgery, vascular malformations and underlying cortical malformations as polymicrogyria; photographic documentation is recommended, particularly if the brain is not being fixed. Other neuropathological causes of sudden death, as acute traumatic brain injury or spontaneous intracerebral haemorrhages and meningitis are usually readily apparent naked eye but should nevertheless be supported with histology to explore aetiology. More focal or subtle neuropathologies, such as fatal colloid cysts or acute encephalitis, can require more careful approach and better identified in fixed brains and often require additional confirmatory immunohistochemistry.

There is no single neuropathological feature that can categorically confirm that seizures occurred during life in the absence of supportive clinical documentation. There are certain pathologies that have strong associations with epilepsy and some patterns of regional neuronal damage and re-organisation (e.g. mossy fibre sprouting, see below) are relatively specific for seizure-related brain injury. Nevertheless, epilepsy is a clinical diagnosis that requires corroborative EEG findings during life. Among lesions that are known to highly associate with epilepsy, published series to date do not suggest that any single pathology type is over-represented in SUDEP. Indeed, the range of pathologies in SUDEP capture those commonly encountered in surgical epilepsy series, including hippocampal sclerosis, cortical malformations such as focal cortical dysplasia (FCD) and low-grade tumours³. Focal neuropathological abnormalities are found in ~50% of SUDEP autopsies, ranging from 34 to 89% between larger SUDEP series. Leestma, identified brain lesions in 60% of SUDEP cases¹⁹⁹, but not all SUDEP studies have replicated this and there are few published large post-mortem non-SUDEP epilepsy series for comparison. Variability in lesion detection in SUDEP may reflect the population demographics under study as well as methodological differences, for example whether only macroscopically visible or additional histological pathologies are reported. Indeed audits have shown that identification and documentation of brain pathology pertaining to epilepsy is highly dependent on the brain being examined in detail following a period of fixation^{200,201}, the number of histological regional samples taken, and the depth of the evaluation, including if immunohistochemistry is performed as recommended in epilepsy surgical protocols^{1,109,202} as well as the experience and training of the pathologist. Furthermore clinical information of investigations localising the seizure focus to a specific brain region (e.g. EEG, seizure semiology, MRI, PET findings) may increase the detection of underlying pathology, especially as some epilepsy pathologies may be macroscopically occult. For example, focal cortical dysplasia and smaller, diffuse cortical tumours.

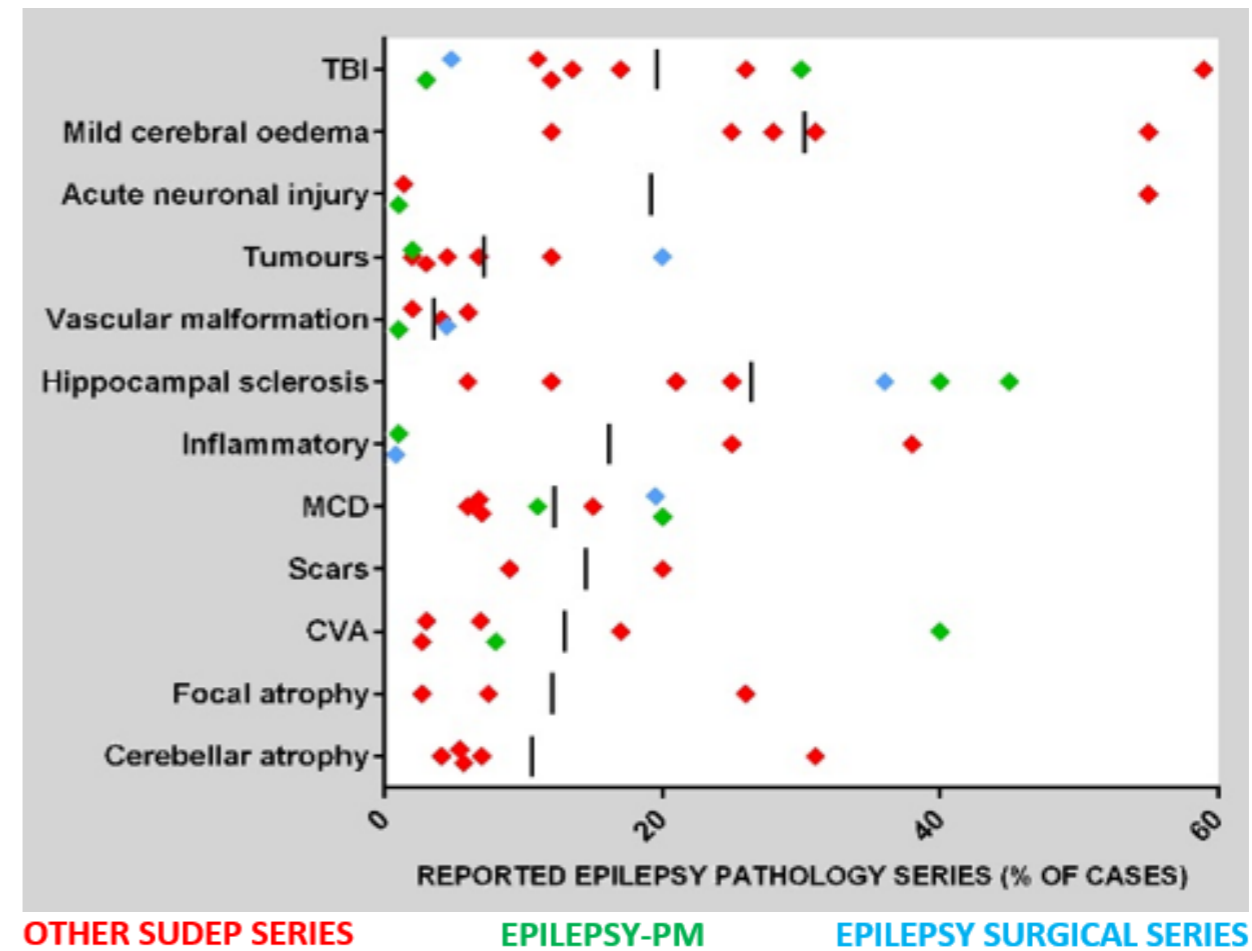


Figure 18: Comparing incidence of reported lesions in SUDEP post mortem series to epilepsy post mortem series and surgical series.

Additional investigations (molecular autopsy and cardiac investigations):

It is highly recommended (and now mandatory in some regions of the UK) that post mortem investigations in paediatric or adult sudden deaths where there is no anatomical or toxicological cause of death, tissue samples should be collected for molecular genetic testing. In Post mortem examination in suspected SUDEP it is requisite to exclude a cardiac cause of sudden death (structural or genetic) with histology where appropriate. Following status epilepticus or a convulsive seizure, stress-induced cardiac changes or *Takotsubo* cardiomyopathy can occur. Although an increased incidence of mild cardiac hypertrophy and fibrosis have been reported in some epilepsy and SUDEP series there is conflicting evidence for this^{203,204}. Nevertheless, careful consideration is advocated for attributing minor cardiac pathologies as the underlying cause of death and categories of possible SUDEP should be considered where there is uncertainty. Furthermore underlying channelopathies and genes causing long QT syndrome (including *KCNQ1*, *KCNH2*, *SCN5A*, *RYR2*, *HCN4*) can cause both epilepsy and arrhythmias or increase the risk of seizure-induced arrhythmias and have been linked to SUDEP (reviewed in reference¹⁹⁴). Consideration should be given to genetic testing in suspected cases at post-mortem and the hereditary implications and organ referral to a cardiac specialist as appropriate. Pulmonary pathology, mainly congestion or oedema, is also frequently reported in 72% of SUDEP post-mortems²⁰⁴. The possible pathogenic mechanisms of pulmonary oedema following seizures include increased sympathetic drive, altered hydrostatic pressures and increased pulmonary capillary

permeability ('neurogenic pulmonary oedema'). It is possible that this, together with central apnoea following a seizure and impaired arousal during sleep, contributes to the sudden death.

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CHAPTER 5

Genetics of the epilepsies

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Introduction

Genetics is a huge and growing area across human biology and medicine, providing information about basic processes from birth to death, from development to degeneration, and in some instances revealing enough about disease biology to lead to rational new therapies or better use of existing treatments. Recent advances in genetic testing are at the heart of current research on the genetic factors influencing drug response and adverse drug reactions in epilepsy. Genetic, and especially genomic, testing is likely to be increasingly used to improve the effectiveness and safety of epilepsy treatments, focusing on each individual and their specific epilepsy according to the 'precision medicine' paradigm. 'Precision medicine' focuses on the identification of an underlying genetic aetiology allowing personalised therapeutic choices.

Genetics can empower all sides in the healthcare setting, from the person with the condition to the physician delivering care. Much has already been written about the experience and perspective of people with epilepsy, and there will be more to come. Physicians are excellent at seeing patterns in their patients: genetics can produce biological explanations for such patterns and for unusual deviations from such patterns. Syndromes become explicable diseases, and clinicians will remain the key element in the translation of genetic discovery to clinic for the benefit of people with epilepsy. The pace of such discovery and the magnitude of the challenge ahead will come as a surprise to most of us. It is therefore important that everyone involved in treating epilepsy should have some grounding in genetics, and in epilepsy genetics. By providing information, probably the most available from any single test, genetics will change our thinking about epilepsy, at least as much as did EEG and MRI. People with epilepsy themselves, and their families and carers, are already pushing ahead. Genetics offers real possibility for meaningful collaboration not just between scientists and clinicians, but also between all parties, including funders, providers and, most of all, those with the conditions.

We have long known that 'epilepsy' is not one condition. Progress in the genetics of the epilepsies is providing a factual landscape for this established diversity of the epilepsies. Today's challenges are not to acquire genetic data, but to interpret the vastness of the data emerging from genetic work in the epilepsies in the context of the even larger universe of genetic data across the life sciences. In this context, this chapter will focus more on concepts than on individual genes. Any printed list of genes linked with an epilepsy is soon dated.

Background

As is well known, a role for genetics has long been postulated in the epilepsies, derived from observations in families. More broadly, the 'neurological trait' is a phenomenon talked about by clinically-astute neurologists for many years (see, for example, Gowers 1885!) – it is, incidentally,

interesting that recent research efforts in genetics are exploring the genetic underpinnings of such phenomena, seeking shared genetic susceptibility across brain diseases, and soon also across somatic co-morbidities. More formal heritability studies, mainly based on twin cohorts, have begun to define and quantify aspects of the genetic contribution to the epilepsies^{2,3}, but have inevitably been limited because we have not really known if the input phenotypic mixes are biologically correct. On this background of belief in a role of genetics in causation, newer technologies have made possible real advances not only in discovery of causes but also discovery in other domains where genetics might have a role – such as susceptibility, specific phenomenological traits, pharmacogenomics and outcomes, as well as co-morbidities and the definition of new syndromes and new categorisation of the epilepsies based on a better understanding of causation.

Current understanding of genetics of the epilepsies

The reorganisation of the epilepsies promulgated in 2010 by the ILAE Commission on Classification and Terminology was predicated on the belief that genetic information in the epilepsies was informing a new understanding based on biological discovery underpinning clinical pattern recognition⁴. The spate of publications in epilepsy genetics over the last few years bears witness to this. The reorganisation was of course controversial, and it is not the case that all the beliefs enshrined in the original reorganisation have been underpinned by actual genetic discovery⁵. Nevertheless, there has been enormous progress, with discoveries in a number of major domains: syndromic epilepsies, epileptic encephalopathies (which may have an overlap of course with ‘syndromic’ epilepsies), progressive myoclonic epilepsies, and a small group of generalised epilepsies and some focal epilepsies. The most recent classification of the epilepsies includes three levels of diagnosis: seizure type, epilepsy type and epilepsy syndrome; according to this new classification, the aetiology should be considered at each step of the diagnostic pathway, as it often carries significant treatment implications⁶. Genetic aetiology is defined as ‘epilepsy that results directly from a known or presumed genetic mutation in which seizures are a core symptom of the disorder’. The epilepsies in which a genetic etiology has been implicated are quite diverse and, in most cases, the underlying genes are not yet known⁶. There has also been much more limited progress in other areas, such as treatment genomics. Most other aspects of the epilepsies, such as outcomes and co-morbidities, have not yet been addressed. Recent progress is reviewed here in terms of concepts, rather than in terms of every gene that has so far been linked to epilepsy.

Discovery in epilepsy genetics, inevitably, has followed technological advances⁷. In the current era, the first new genetic technology that became widely available was array comparative genomic hybridisation (aCGH), which permits comparison of segments of a patient’s DNA with, typically, pooled DNA from a group of controls without the same condition, usually healthy individuals. The technique highlights segments where the number of copies of that segment is different to that seen in controls (copy number variation), down to a certain size resolution, usually of the order of a few hundred kilobases, but occasionally with higher resolution. aCGH is indicated when the presenting epilepsy is syndromic, being associated with other features, such as facial or somatic dysmorphism, intellectual disability, autism spectrum disorder or multiple co-morbidities. Microdeletions and microduplications (together falling within the category of copy number variants, CNVs) have been increasingly reported in association with complex epilepsies⁸⁻¹⁵ and have sometimes pointed to novel candidate epilepsy genes¹⁶. Depending on case series and criteria for inclusion, about 12% of people with complex epilepsy might have a CNV considered relevant. A recent multicenter study of over 1000 patients with ‘epilepsy plus’ phenotype, defined as epilepsy with comorbid features, including intellectual disability, psychiatric symptoms, and other neurological and nonneurological features, identified pathogenic and possibly pathogenic autosomal CNVs in nearly 13% of cases¹²³. Interestingly, aCGH has also proved informative for some groups of ‘genetic’ (idiopathic) generalised epilepsies. The paper that many consider to herald the current era of genetic discovery in epilepsy reported the first CNV associated with a common epilepsy, 15q13.3 microdeletion, seen

in 12 patients in the classic 2009 report by Helbig *et al*⁷. The same CNV has now been studied in a 246-case series, 28% of whom had seizures¹⁸; neuropsychiatric manifestations were common, major congenital malformations were not. Further genotype-phenotype correlation with long-established CNVs associated with epilepsies will become possible as increasing numbers of cases are reported. Such phenotypic delineation will facilitate genetic screening and interpretation for future practice. CNVs have also been identified in genetic generalised epilepsies, with or without intellectual disability^{19,20} L.M.D., brain malformations and refractory epilepsy²¹, typical and atypical Rolandic epilepsy²².

At the leading edge of current research in epilepsy genetics, and the most productive tool in terms of gene discovery, is whole exome sequencing (WES) which is increasingly becoming part of routine clinical practice. With falling costs and increasing availability, an even wider range of epilepsies, more or less homogeneously grouped, have been subjected to WES. Discoveries are being reported at a pace too great to meaningfully list each individually. Progress has been most dramatic for the epileptic encephalopathies. Though individually rare, the encephalopathies account for an important part of the burden of the epilepsies. Their genetic tractability is probably because they are often caused by variants of large effect, which is perhaps not surprising considering the severity of the phenotype. Although for some specific genetic encephalopathies, distinctive electroclinical features and comorbidities have been delineated, there remains a significant degree of genetic and phenotypic heterogeneity. A set of genes and related pathways responsible for a number of epileptic encephalopathies was reported using trio exome sequencing²³ – several known ‘epilepsy genes’ were identified, and a number of novel candidates were proposed. Also, a number of studies have used combined CNV surveys and WES analysis to identify pathogenic CNVs in epileptic encephalopathies²⁴⁻²⁷. One candidate, *DNM1*, was then confirmed by merging data from consortia²⁸, illustrating the frequent need for large numbers of patients to formally declare involvement of a given gene. Mutations in many genes have been identified in the epileptic encephalopathies, including for example *AARS*²⁹, *CDKL5*³⁰, *KCNA2*³¹, *STX1B*³², *PURA*³³, *WWOX*³⁴, *SLC13A5*³⁵, *DOCK7*³⁶ and *SZT2*³⁷ among many others. Some of these conditions have distinctive features, but in most cases there is a spectrum of clinical variability ranging from self-limited epilepsy to severe epileptic encephalopathy, such as in phenotypes associated with mutations in *SCN1A*³⁸, *SCN2A*³⁹, *SLC2A1*⁴⁰, *KCNQ2*⁴¹, and *KCNA2*⁴². In an epileptic encephalopathy, the epileptiform activity interferes with development resulting in cognitive slowing and often regression, and amelioration of the epileptiform activity may have the potential to improve at least some of the developmental consequences of these disorders. On this basis, identification of the single gene dysfunction causing an epileptic encephalopathy may be crucial to select a targeted treatment, if available, and improve the prognosis as a consequence. More and more genes associated with an epileptic encephalopathy have been identified in large cohorts through whole exome or targeted sequencing^{23,28,43-46}, and currently a genetic diagnosis can be made for about ~10-40% of patients tested clinically^{47,124-125}. In addition, there are likely to be features of the encephalopathy unimproved by seizure control. Candidate gene selection in the epileptic encephalopathies therefore remains a challenge, making gene panels for clinical genetic diagnosis of limited value, compounded by the rapid pace of gene discovery: a gene may not be considered a candidate for the panel, or not be included because it was not linked with epilepsy at the time of panel design. A further implication is that genotype-phenotype correlation is needed, but will also be challenging, and may need newer phenotyping tools accessing data not typically used in clinical phenotyping⁴⁸. Moreover, given the richness of the emerging data, there is considerable scope for data mining and novel analytic methods, some to predict new genes for epileptic encephalopathy⁴⁹, with methods also to prioritise genes^{50,51}. The greatest promise lies perhaps in the identification of pathways implicated across sets of epileptic encephalopathies, such as the mTOR pathway⁵², that may already have possible directed treatments or repurposable drugs, or that might point the way to new generic treatments relevant across epileptic encephalopathies linked by shared mechanisms^{23,53}. Currently, drug therapies targeted to the underlying genetic cause are available for only a minority of genetic epilepsies^{54,55,126}.

WES, and other methods, have also been successful in identifying the cause(s) of some rare conditions which may feature epilepsy as part of a phenotype. Examples include alternating hemiplegia of childhood (due in 80% of cases to *de novo* mutation in the *ATP1A3* gene⁵⁶), in which rare condition perhaps 50% of affected individuals have seizures; DOORS syndrome, which is very rare, due in about 50% of cases to mutation in *TBC1D24*⁵⁷, and for which genotype-phenotype correlation may yet show it can be considered in some cases an epileptic encephalopathy⁵⁸; and epilepsies with other comorbid features such as migraine or movement disorders, for which implicated genes include *SCN1A*, *CACNA1A*, *ATP1A2*, *SLC2A1*, *PRRT2*, *STXBPI* and *FOXG1*⁵⁹⁻⁶³. Of considerable interest are the epilepsies with associated language or speech disorder – these are broad summary terms for aspects of the phenotype that have often been characterised in great detail, within the epilepsy-aphasia spectrum. Mutations have been identified in the NMDA receptor NR2A subunit-encoding gene *GRIN2A* in Landau-Kleffner syndrome, electrical status epilepticus in sleep (ESES)/continuous spike and wave during slow-wave sleep syndrome (CSWSS), and typical and atypical rolandic epilepsies⁶⁴⁻⁶⁶. Another example of genetic epilepsy with important clinical consequences is the *COL4A1/COL4A2*-related disease, where there are typically abnormalities on neuroimaging, and the severity of clinical phenotype tends to worsen in succeeding generations, particularly when maternally inherited¹²⁷.

The progressive myoclonic epilepsies (PMEs) were amongst the most successfully studied from a genetic perspective even before WES. Genetic discovery has proved demonstrably valuable in understanding disease biology, especially for example for Lafora disease and Unverricht-Lundborg disease⁶⁷, though breakthroughs in treatment options are still awaited. There have been further discoveries in the PMEs, some of which could be considered surprising. ‘North Sea’ progressive myoclonus epilepsy has been found to be due to homozygous mutation in *GOSR2*, and has a distinctive phenotype, with all patients having a progressive and relentless course, and all developing scoliosis by adolescence, sometimes with other skeletal findings⁶⁸. A systematic examination of 84 unsolved PME cases using WES as the discovery tool found causal mutation in 31%⁶⁹. Most interestingly, a recurrent *de novo* mutation was found in an ion channel gene (*KCNK1*) and identified as a new major cause for PME, with eleven unrelated exome-sequenced (13%) and two affected individuals in a secondary cohort (7%) carrying this mutation. *KCNK1* encodes a subunit of voltage-gated potassium ion channels, which have major influence on high-frequency neuronal firing. The detected recurrent mutation causes a dominant-negative loss-of-function effect. Other cases within this cohort that had not been explained were found to have pathogenic mutations in known PME-associated genes (*NEU1*, *NHLRC1*, *AFG3L2*, *EPM2A*, *CLN6* and *SERPIN1*), while unsuspected mutations were identified in other genes that had previously not been linked to epilepsy and/or PME, including the *TBC1D24* gene. Some PMEs are very rare, caused by private mutations in single families, for example PME due to *PRICKLE1* mutations⁷⁰. Other PMEs are allelic to previously known PMEs, for example, the most common form of Kufs disease is allelic to the late-infantile variant neuronal ceroid lipofuscinoses, *CLN6*¹²⁸. Mutation in the *KCTD7* gene, encoding a member of the potassium channel tetramerization domain-containing protein family, have been associated with progressive myoclonic epilepsy (EPM3) and neuronal ceroid lipofuscinosis (*CLN14*). *KCTD* protein family members lack predicted channel domains. Recently biallelic *KCTD7* mutations have been identified as causative of a distinct neurodegenerative disorder with lipofuscin and lipid droplet accumulation but without defining features of neuronal ceroid lipofuscinosis or lysosomal storage disorders, and *KCTD7* deficiency appeared to cause an underlying autophagy-lysosome defect also observed in yeast¹²⁹. It is fascinating that while WES is increasingly identifying genes that do not encode ion channels in other epilepsies, in the PMEs which have not traditionally been considered channelopathies, WES has revealed the involvement of an ion channel, and other genes for which PME was not considered part of the phenotypic spectrum before. This discovery further compromises the idea of gene panels as currently conceptualised.

Recently expansions of noncoding TTTCA and TTTTA pentanucleotide repeats, irrespective of

the genes in which the expanded repeats are located, were identified as the genetic cause of some cases of familial adult myoclonic epilepsy (FAME), a highly-penetrant autosomal dominant condition featuring cortical tremor and epilepsy with infrequent seizures (mainly generalised tonic-clonic seizures)¹³⁰⁻¹³¹. The mechanism through which repeat expansion in non-coding regions gives rise to neurotoxicity has yet to be established.

Despite the clear indications from both epidemiological, and early molecular, genetic studies of probable significant genetic contribution to the genetic generalised epilepsies, such as juvenile myoclonic epilepsy, juvenile absence epilepsy and childhood absence epilepsy, there are still very few genes definitively linked to these phenotypes. In early-onset absence epilepsy, mutations in the *SLC2A1* gene, encoding a cerebral glucose transporter and causing GLUT1 deficiency, were reported in one study in about 10% of cases⁷². Subsequently, a review of seven studies identified *SLC2A1* mutation in 2.4% (29) of 1110 patients with generalised epilepsies overall, with a higher rate (5.6%) among 303 patients with early-onset absence epilepsy⁷³. Clues to a possible *SLC2A1* mutation were the additional presence of abnormal movements or a family history of seizures, abnormal movements, or both. As GLUT1 deficiency can be treated with the ketogenic diet, it is important to identify its presence. No other glucose or lactate transporters have been implicated in early-onset absence epilepsy⁷⁴, and no other generalised epilepsies have been shown to be due to *SLC2A1* mutation⁷⁵. Mutations or deletions in a variety of genes have been identified in genetic epilepsy with febrile seizures plus (previously known as generalised epilepsy with febrile seizures plus, both GEFS+), including *SCN1A*, *PCDH19*, *SCN1B*, *SCN2A*, and *GABRG2*⁷⁶⁻⁷⁸. Rare coding variants in genes encoding GABA_A receptors subunits have been shown to represent a significant risk factor for genetic generalised epilepsies¹³². But most cases of all of these epilepsy types, that is the vast majority of genetic generalised epilepsies, remain genetically unexplained, even with systematic WES. It has also recently been shown that the involvement of *EFHC1* in juvenile myoclonic epilepsy needs to be reconsidered⁷⁹, with a number of lines of enquiry raising doubts about the pathogenicity of detected mutations, as nicely outlined in a sobering reminder that the standards for declaring causality must be robust and that supporting evidence should be multidimensional⁸⁰. The genetic generalised epilepsies remain a conundrum, with ‘genetic’ in the currently-recommended name, but little ‘genetic’ in terms of actual genes.

Progress has been made also in the focal epilepsies. Perhaps most interesting, and what may possibly emerge as the most common genetic cause in familial focal epilepsies, is the discovery of mutations in *DEPDC5* in several familial and sporadic epilepsy phenotypes, including familial focal epilepsy with variable foci, familial temporal lobe and autosomal dominant nocturnal frontal lobe epilepsies, rolandic epilepsy and other non-lesional focal childhood epilepsies, and focal epilepsy associated with focal cortical dysplasia⁸¹⁻⁸⁵ Institut du Cerveau et de la Moelle Epinière (ICM). These findings are of especial interest as *DEPDC5* is part of the mTOR pathway⁸⁶, activity within which can be manipulated using the existing drug rapamycin. *DEPDC5* mutations have also been shown in epilepsies with developmental malformation⁸⁷. Somatic mutations in *MTOR* itself have been reported in focal cortical dysplasia and hemimegalencephaly⁵². In addition to *DEPDC5* and *MTOR*, additional mTOR pathway genes have been associated with the pathogenesis of focal epilepsies, and predisposition to sudden unexpected death in epilepsy (SUDEP).¹³³⁻¹³⁴ Mutations in the ion channel gene *KCNT1* have been reported in malignant migrating partial seizures of infancy and sleep-related hypermotor epilepsy (SHE)^{88,89}. Genes encoding neuronal acetylcholine nicotinic receptor subunits, including *CHRNA4*, *CHRNA2*, and *CHRN2*, are also implicated in the pathogenesis of SHE¹³⁵. Most focal epilepsies, however, remain genetically unexplained.

A case-control whole exome sequencing study of a large collection of data from patients with one of the two most common epilepsy syndrome groups, genetic generalised epilepsy and non-acquired focal epilepsy, was conducted to search for ultra-rare deleterious variants, and compared the qualifying variant rates found in these cases to background rates estimated from sequenced

controls⁹⁰. The sequence data from 640 individuals with familial genetic generalised epilepsy and 525 individuals with familial non-acquired focal epilepsy were compared to the same group of 3877 controls, and found significantly higher rates of ultra-rare deleterious variation in genes already established as causative for dominant epilepsy disorders. Significant enrichment of ultra-rare variation in known epilepsy genes shows an important connection between the genetics of common and rare epilepsies, and shows that the many variants responsible for epilepsy risk are very rare in the general population. These results suggest that the proposed paradigm of targeting of treatments to the genetic cause in rare devastating epilepsies might also extend to a proportion of common epilepsies.

Finally, there are of course also the epilepsies across the spectrum with well-established genetic causation. These epilepsies include those associated with developmental structural abnormalities, neurocutaneous disorders, chromosomal disorders established well before the aCGH era, several PMEs, neurometabolic disorders, mitochondrial cytopathies, the focal epilepsies, autosomal dominant frontal lobe epilepsy and lateral temporal lobe epilepsy, Dravet syndrome, Rett and related syndromes. Several excellent reviews have been published on these conditions. It is also worth noting that not all cases with phenotypes similar or related to these epilepsies have actually been solved and efforts continue to explain these. Just to give two examples, new genes have been identified for Dravet syndrome (such as *CHD2*⁹¹) and for polymicrogyria (such as *CCND2*⁹²) in various settings.

Beyond the discovery of genetic causes of specific types of epilepsy, other aspects of the epilepsies are also being investigated. Given the breadth of phenotypic variation seen in some otherwise characteristic epilepsies, there has been much interest in genetic modifiers of phenotype. Identifying modifiers is challenging as many factors other than genetic variation may play a role. Animal models have been explored from this perspective, with evidence for example that mutations in different genes may influence the epileptic phenotype⁹³. In humans, *SCN9A* has been proposed as a modifier of the Dravet and GEFS+ phenotypes⁹⁴. Some have considered microdeletions to be modifiers within genetic generalized epilepsy phenotypes⁹⁵. Taking this concept further, network disruption has been proposed in mesial temporal lobe epilepsies with hippocampal sclerosis⁹⁶. Cause and effect can be difficult to disentangle in such studies, and the standards for proof are yet to be clarified in this area. The provocative effect of intermittent photic stimulation in precipitating seizures has been a topic of genetic research for many years. The area is complex, with definitions and protocols varying between studies, sites and publications. Taking broad common phenotypes into account, and based on the observation that photosensitivity is frequently present in epileptic encephalopathy due to *CHD2* mutation or deletion⁹⁷, it was shown that *CHD2* mutation was also present in a small proportion of people with photosensitivity and more common epilepsies, and was present in 3/36 patients with the syndrome of eyelid myoclonia with absences⁹⁸.

Treatment genomics in the epilepsies remain a challenge. In keeping with most trials, most studies have been drug-centred. Variants significantly increasing the risk of severe or mild rash on exposure to carbamazepine have been identified in the HLA system, with *HLA-B*15:02* being a major risk in populations of South Asian extraction⁹⁹ and *HLA-A*31:01* in people of European extraction¹⁰⁰. Screening for the *B*15:02* variant has been shown to be cost-effective in a south Asian population¹⁰¹. A systematic review has shown that *HLA-B*15:02* in Asian patients is associated with a pooled odds ratio of 113.4 for severe carbamazepine-induced reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), and that 461 patients would need to be screened for *HLA-B*15:02* to prevent one episode of such a severe reaction¹⁰². For *HLA-A*31:01*, which is more broadly associated with cutaneous hypersensitivity reactions to carbamazepine across multiple ethnicities, this study estimated that between 47 and 67 patients would need to be tested to prevent one episode of hypersensitivity¹⁰². For phenytoin, the *CYP2C9* missense variant rs1057910 (*CYP2C9*3*) was significantly associated with severe cutaneous adverse reactions, an intriguing

finding¹⁰³. Phenytoin-induced maculopapular exanthema, another specific cutaneous adverse reaction common to antiepileptic drugs, has been associated with rare variants in the complement factor H-related 4 (*CFHR4*) gene and in the complement factor H (*CFH*) gene¹³⁶. Apart from these few findings for severe skin reactions, there are no other clearly established pharmacogenomic findings in epilepsy currently⁵⁵.

For discoveries beyond severe adverse reactions, and more seizure control genomics, it may be that the strategy will need to change focus from a drug-centred approach to a patient-centred approach, despite the challenges that studies based on small numbers of patients raise, both in terms of proof and regulatory requirements. There are already a few additional examples where genetic findings of course have treatment implications. The best example is the finding of an *SCN1A* mutation in an appropriate phenotype, such as Dravet syndrome, which should usually lead to the withdrawal of sodium channel-blocking antiepileptic drugs and consideration of valproate, benzodiazepines, and other agents including stiripentol¹⁰⁴. In the appropriate clinical contexts, which may be wide, other examples include: identification of an *SLC2A1* mutation leading to use of the ketogenic diet^{74,105-107}; in *PNPO* or *ALDH7A1* mutation, supplementation with pyridoxine or pyridoxal 5'-phosphate¹⁰⁸; with *FOLR1* mutation, use of folinic acid¹⁰⁹. Novel therapies have been explored at some level in newer genetic epilepsies. Recent data suggest that fenfluramine, initially developed as an appetite suppressant but withdrawn from the market due to serious adverse effects, may be effective in Dravet syndrome^{110,111}. Fenfluramine has serotonergic effects¹¹², but the exact anti-seizure mechanism has not been elucidated yet. Currently there are four ongoing clinical trials to evaluate the effectiveness and tolerability of this drug in Dravet Syndrome. *KCN77*-associated epilepsies were described in 2012; in 2014, reversal of mutation-associated gain-of-function was reported in a *Xenopus* oocyte model using a drug (quinidine) previously used in humans, though not one known to be an antiepileptic¹¹³. *GRIN2A* mutations were reported in association with various epilepsies in late 2013; in 2014, functional analysis of one mutation showed that the mutated protein retained sensitivity to a known blocker (memantine) of this channel, which also reduced seizure frequency in the single patient carrying the mutation¹¹⁴. Preliminary data from humans with *KCNQ2*-related epilepsy, where most analysed mutations showed a dominant-negative effect on wild-type *KCNQ2* subunits¹¹⁵, suggest retigabine may be a useful treatment option⁴¹; sodium channel blockers are also effective in *KCNQ2*-related epilepsy¹¹⁶, possibly because of the co-localization at the neuronal membrane of voltage-gated sodium and potassium channels¹¹⁷. There is clinical evidence of a possible effective precision medicine approach in using sodium channel blockers to treat patients with *SCN2A*- and *SCN8A*-related epilepsy, in particular if the mutations are known to cause gain of function, although the mechanism of the effect has not been elucidated yet^{118,119}. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been used for various benign tumours associated with tuberous sclerosis complex (TSC), where epilepsy is the most common neurologic symptom in patients with TSC¹²⁰. A phase 3, randomised, double-blind, placebo-controlled study has recently showed that adjunctive everolimus treatment significantly reduced seizure frequency with a tolerable safety profile in drug-resistant focal epilepsy associated with TSC¹²¹. A genome-wide association study has suggested a genetic predisposition for response to the ketogenic diet in drug-resistant epilepsy.¹³⁷ However, the only established genetic factors predisposing to good response in humans are mutations in *SLC2A1* causing GLUT1 deficiency syndrome and some other very rare neurometabolic conditions.

Current tools, models and problems

The landscape of epilepsy genetics is changing rapidly – which overall is likely to be to the benefit of people with epilepsy. For the clinician, the tools available for genetic diagnosis are aCGH, candidate gene testing, and gene panels. Array CGH applied in an appropriate clinical setting may identify a pathogenic copy number variant in perhaps 12% of cases, as discussed above. Candidate gene testing requires the clinician to have knowledge of the gene(s) which may be altered to

produce the observed phenotype. Some epilepsies have a very characteristic phenotype, and gene selection may be obvious. Candidate gene testing typically uses Sanger sequencing, to which methods such as multiplex ligation-dependent probe amplification may be added for detecting exonic-level changes, such as exonic deletions. Dravet syndrome is amongst the best examples: with a typical history, over 80% of cases will have a pathogenic change in the gene *SCN1A*. Other genes when mutated can cause a Dravet-like phenotype, while having an *SCN1A* mutation does not mean a patient has Dravet syndrome unless the phenotype is appropriate: recent guidelines for *SCN1A* testing should help in these situations¹²², and may be needed for other genes – another challenge for the years ahead. Gene panels partly sidestep this issue of complex and overlapping genotype-phenotype correlation, but have important limitations of their own, and are likely to be a step in the evolution of genetic testing in epilepsy. Next-generation sequencing, reading much more of the available genetic information, is already being applied in a few settings. Next-generation based panels are in use and may be informative, but WES is still to be broadly used in epilepsy genetics. CNVs can be difficult to pick up through WES, and aCGH, or genotyping arrays, may still retain a role in clinical practice even when WES becomes more widely applied. Eventually, it seems likely that whole genome sequencing (WGS), will become a standard clinical tool, as it can significantly increase yield.

For clinicians, it is important to consider genetic testing as part of the armamentarium that can be used to better understand epilepsy in an individual. Genetic testing should be considered alongside other investigations such as MRI and EEG. WES and WGS are where MRI was 20 years ago – available only in specialist centres if at all, and still presenting important challenges in analysis and interpretation. As with MRI, it seems likely that WES or WGS will become part of the clinical investigation of many more people with epilepsy, to inform understanding of causation, prognosis, treatment, and co-morbidities. The model for genetics should change from its use in occasional cases, to its integration into routine practice as a source of important individual information that alters management. While the current focus is on the genetic code, other aspects of genetic information, such as the control of gene expression through epigenetic regulation, the role of a variety of RNA species and translational modifications, may also eventually prove important, though the need for organ-specific testing makes these avenues hard to explore, at least currently. Moreover, even current and imminent technologies that may advance knowledge will present hurdles. Such issues range from the conceptual, even for familial epilepsies where the condition may be Mendelian, but not necessarily monogenic, to practical considerations such as how the mass of data emerging from genetic testing will be stored, who will have control over its use, how such truly big data will be analysed, how results will be interpreted in the context of the individuals rather than populations, how the relevance of complex gene networks can be judged in an inaccessible organ part way through the natural history of an individual's epilepsy, and how all this can be managed in an appropriate and just ethical and social environment. At the very least, it seems likely that to realise the full benefits from genomic data in clinical practice will require a multidisciplinary team and changed models of management, which will allow, albeit carefully regulated, individual-level drug repurposing. Among the best outcomes, perhaps we can also hope that epilepsy genomics will also bring better care for the vast majority of people with epilepsy across the world who today do not have access to any care at all. The genome is, after all, our shared heritage.

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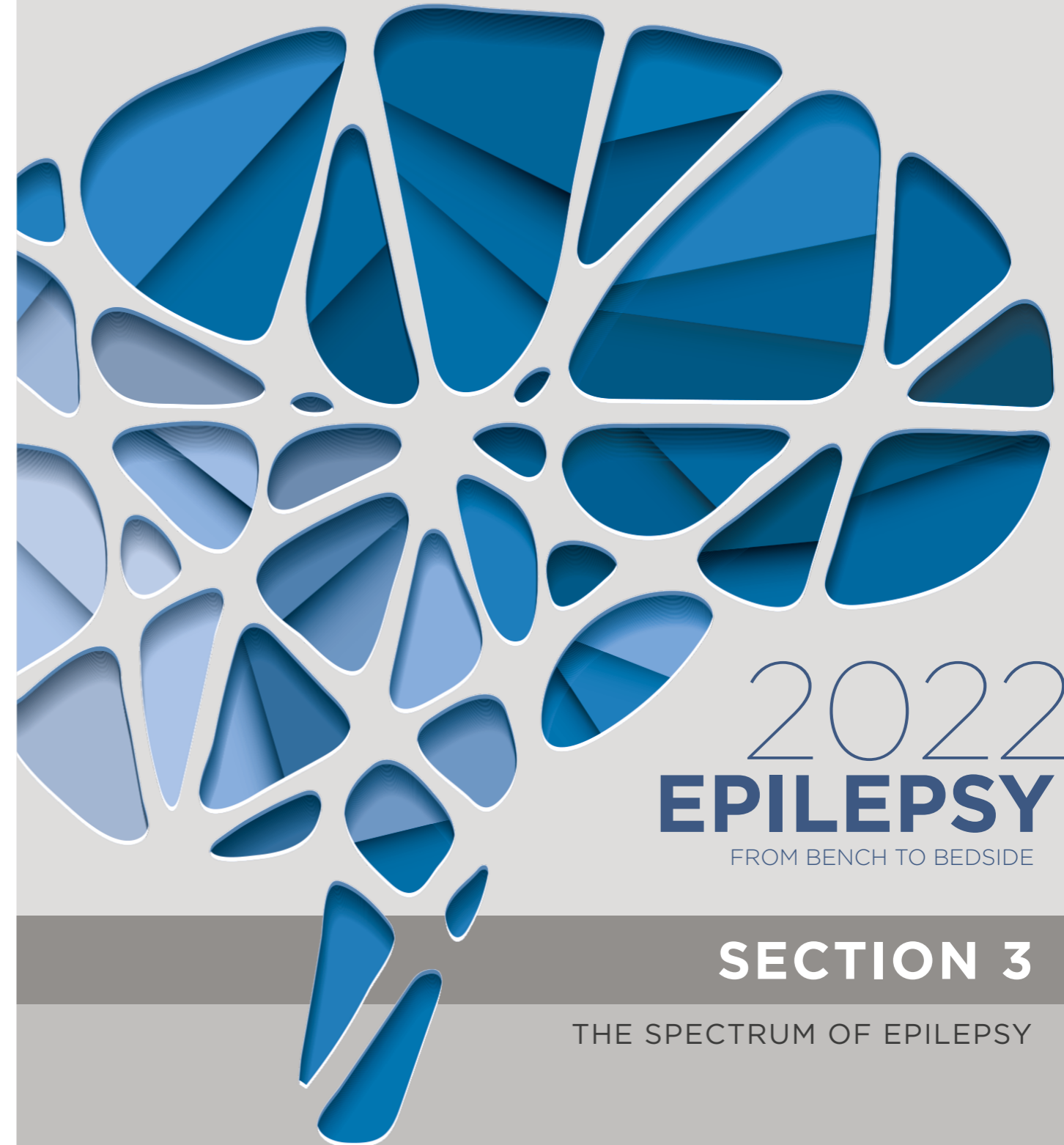
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2022
EPILEPSY
 FROM BENCH TO BEDSIDE

SECTION 3

THE SPECTRUM OF EPILEPSY

CHAPTER 6

Neonatal seizures

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Introduction

The immature brain seems more prone to seizures than the more mature brain. Seizures are more common in the neonatal period than during any other time throughout life. Seizures in the neonatal period are also the most common neurological emergency and are associated with high mortality and morbidity^{1,2}.

The incidence of seizures in infants born at term is 0.5–3 per 1000 live births; the incidence is even higher in preterm infants, ranging from 1–13% of very low birthweight infants³. Variations of described numbers of incidence can be explained by different diagnostic definitions and methods used. Most of these epidemiological studies include only clinical seizures. The exact incidence of electrographic, clinically silent seizures is as yet unknown. The majority of neonatal seizures occur on the first day, and 70% of all cases eventually recognised have been diagnosed by the fourth day.

Aetiology

In contrast to seizures in infancy and childhood, most neonatal seizures are acute and symptomatic with suspected specific causes; relatively few seizures are idiopathic or part of a clearly defined epilepsy syndrome. Although many causes can give rise to neonatal seizures (Table 1), although only a few of these conditions account for most seizures. Few seizures are idiopathic. Several decades ago, late hypocalcaemia due to a low calcium:phosphate ratio in baby formula was a frequent cause of neonatal seizures but this is very rare today. At term, hypoxic ischaemic encephalopathy is the most common underlying factor, typically with onset 6–8 hours after the hypoxic insult but within the first 24 hours of life. In preterm infants, cerebrovascular events are the most common cause. Meningitis, focal cerebral infarction, metabolic disorders and congenital abnormalities of the brain can cause seizures at any gestation.

Mechanism

The developing brain is particularly susceptible to developing seizures in response to injury; several mechanisms are likely to be involved. Overall the hyperexcitable state of the immature brain is based upon enhanced excitatory neurotransmission, paucity of inhibitory mechanisms, developmental expression of neuronal ion channels, age-dependent modulation of neuropeptides and age-dependent early microglial activation. In the immature brain there is a relative excess of excitatory neurotransmitters and receptors^{6,7}. The arborisation of axons and dendritic processes as well as myelination are incomplete in the neonatal brain resulting in weakly propagated, fragmentary seizures whose electrical activity may not spread to surface EEG electrodes.

Table 1. Causes of neonatal seizures³⁻⁵.

Cause	Frequency
Hypoxic-ischaemic encephalopathy	30-53%
Intracranial haemorrhage	7-17%
Cerebral infarction	6-17%
Cerebral malformations	3-17%
Meningitis/septicaemia	2-14%
Metabolic	
Hypoglycaemia	0.1-5%
Hypocalcaemia, hypomagnesaemia	4-22%
Hypo-/hypernatraemia Inborn errors of metabolism (such as pyridoxine dependency, folinic acid-responsive seizures, glucose transporter defect, non-ketotic hyperglycinaemia, propionic aciduria)	3-4%
Kernicterus	1%
Maternal drug withdrawal	4%
Idiopathic	2%
Benign idiopathic neonatal seizures	1%
Neonatal epileptic syndromes	
Congenital infections	

Generalised tonic-clonic seizures are rare in the first month of life and not seen in the preterm infant. Neonatal seizures are usually focal, often short lasting (see EEG, Figure 1). The development within the limbic system with connections to midbrain and brainstem is more advanced than the cerebral cortical organisation, leading to a higher frequency of mouthing, eye deviation, and apnoea in neonates than seizures in adults.

Clinical manifestation and classification

Even among trained observers, clinical neonatal seizures may be difficult to recognise and differentiate from either normal behaviours or abnormal movements of non-epileptic origin⁸. Additional problems arise when the relationship between clinical and electroencephalographic seizures is considered. At times, there is temporal overlap of the two (so-called ‘electroclinical seizures’). However, in some clinical settings up to 85% of electrographic seizures are clinically silent (i.e. only electroencephalographic seizure activity present with no clinical accompaniment, referred to as ‘electrical only seizures’), leading to significant underestimation of seizure burden⁹. For these reasons, in the broadest terms a seizure in this age group is best defined either in clinical terms as an abnormal paroxysmal event (with or without EEG seizure activity) or electrographically as a sustained epileptiform change in the EEG, which may or may not be accompanied by paroxysmal alteration in neurological function.

As aetiology and presentation of neonatal seizures is different to seizures in older children and adults, they do not easily fit into the 1981 ILAE classification of epileptic seizure types or the 1989 ILAE classification of epilepsy syndromes and epilepsies⁶². While this continues to be a widely accepted view, the most recently proposed ILAE (The International League Against Epilepsy)⁵⁵ classification suggested that neonatal seizures should not be considered a distinct seizure type, but could be classified within its more general, universal scheme – which would classify all neonatal seizures as either ‘focal seizures’ or ‘other’⁵⁵. Several classifications have been proposed, of which the classifications by Volpe³ (according to clinical features only) and by Mizrahi and Kellaway^{4,10} (according to pathophysiology: epileptic or non-epileptic origin) are more widely used (Table 2).

Table 2. Classification of neonatal seizures.

(1) adapted from Volpe³

Type	Characterisation	Ictal EEG abnormalities
Subtle	Ocular, oral-buccal-lingual, autonomic, apnoea, limb posturing and movements	Variable
Clonic	Repetitive jerking, distinct from jittering. Unifocal or multifocal	Common
Myoclonic	Rapid isolated jerks. Focal, multifocal or generalised	Common if generalised, uncommon if focal
Tonic	Stiffening. Decerebrate posturing. Focal or generalised	Common if focal, uncommon if generalised

(2) adapted from Mizrahi and Kellaway^{4,10}

Type	Characterisation	Epileptic origin
Focal clonic	Rhythmic muscle contractions	✓
Focal tonic	Sustained posturing of limb/trunk	✓
Myoclonic	Random single contractions	✓/-
Spasms	Flexor or extensor, ± in clusters	✓
Electrographic	By definition no clinical correlate	✓
Generalised tonic	Sustained symmetric posturing	-
Motor automatism	Ocular, oral-buccal-lingual or progression movements of limbs	-

The Mizrahi classification has the advantage that it takes the origin of events into account and includes clinically silent electrographic seizures. According to the Volpe classification seizures can be subtle, myoclonic, clonic or tonic. Subtle seizures are the most common seizure type in both preterm and term babies. Manifestations include:

- Ocular phenomena (staring, blinking, eye deviation, eye opening)
- Oral phenomena (mouthing, chewing, sucking, smiling)
- Autonomic phenomena (change in blood pressure and/or heart rate, pallor, increased salivation or secretions; central apnoea occurring rarely as the only seizure manifestation)
- Fragmentary body movements (limb posturing, swimming, pedalling).

Similar phenomena and motor behaviours occur in neonates, especially in premature infants and encephalopathic infants. Although they are often less stereotyped and may be suppressed by restraints or triggered by stimulation, these are clinically very difficult to diagnose⁵. Prolonged video-EEG has clearly shown that the majority of infants with subtle seizures will exhibit ictal rhythmic epileptiform activity^{4,11}. The absence of ictal EEG discharges makes an epileptic origin of these movements less likely. This issue has been addressed in the Mizrahi classification: motor automatisms without clonic or tonic components and without EEG correlate are not considered to be of epileptic origin.

Clonic seizures can be focal, multifocal migrating from limb to limb or, rarely, hemiconvulsive. Jacksonian march is exceptional in neonates, but may be seen in babies with stroke. These seizures are most likely to be correctly diagnosed clinically¹². However, they may be difficult to differentiate from non-epileptic movements, like jitteriness, tremors or shudders. These non-epileptic movements can be suppressed by gentle restraint and may be enhanced by sensory stimuli. There is good correlation with EEG changes.

Erratic, fragmentary or more generalised myoclonic jerks are often associated with tonic spasms, with multifocal clonic or tonic patterns, or with mixed seizure types. They may persist into infancy (infantile spasms). Myoclonic seizures can easily be distinguished from benign neonatal sleep myoclonus by the absence of myoclonia during wakefulness and a normal EEG.

Focal tonic seizures are characterised by stereotyped, abrupt or slower tonic posturing of limb, and/or trunk or eyes, often accompanied by apnoea, flushing, or mild cyanosis. The EEG background is often abnormal and ictal discharges are common. Although still considered in the Volpe seizure classification, generalised tonic posturing is unlikely to be epileptic seizures, but rather to represent transient decerebrate or decorticate posturing, which can be triggered by stimulation and show no ictal EEG correlates. EEG background activity is severely abnormal and the outcome is poor. This seizure type is not classified as being of epileptic origin in the Mizrahi classification.

A characteristic feature of neonatal seizures is the phenomenon of electro-clinical dissociation: seizures can be electroclinical, electrographic (subclinical) or clinical only¹³. The significance of clinical only seizures is unclear. There is an ongoing controversy as to whether electrical-only seizures have an impact on long-term outcome and thus require treatment or not. There is now evidence that they have a similar impact on long-term outcome as electro-clinical seizures¹⁴.

Traditionally, the ILAE has also included some neonatal epileptic syndromes in its classification⁶¹. Most recently, the ILAE proposed a revised syndromic classification that now includes: benign neonatal familial seizures, early myoclonic encephalopathy (EME), and Ohtahara syndrome (early infantile epileptic encephalopathy, EIEE)⁵⁵. These will be discussed later.

Investigations

The large differential diagnosis following a neonatal seizure (Table 2) demands that the initial investigations should concentrate on the common aetiologies requiring prompt specific treatment. Certain clues to the aetiology may be present, such as a history of perinatal asphyxia or maternal narcotic abuse, but other causes such as hypoglycaemia, hypocalcaemia, and CNS infection may coexist and need excluding. Investigations include:

- Septic screen, including blood cultures and lumbar puncture
- Laboratory: always glucose, electrolytes, blood gas, packed cell volume, if necessary bilirubin, ammoniac, metabolic screening, TORCH, screening for drug abuse
- Consider therapeutic trial of pyridoxine and pyridoxal phosphate
- Always cranial ultrasound scanning, consider MRI
- EEG.

Neuroimaging

Cranial ultrasound scanning is readily available in most centres and is useful as a first-line imaging investigation for exclusion of gross CNS pathology (CNS malformations, periventricular haemorrhage). If initial ultrasound examination is normal, but the infant continues to have seizures or has abnormal inter-ictal neurological signs, a CT or MRI examination has to be carried out to detect other forms of clinically important pathology, such as cerebral infarction, subdural and subarachnoid haemorrhage or cerebral malformations.

EEG

EEG definitions vary, but paroxysms are considered to be seizures if they last more than 10 seconds. Neonatal electrographic seizures are often not sustained. The typical duration of the electrographic neonatal seizure is 2–3 minutes¹⁵, but many seizures will be shorter, particularly in preterm infants¹⁶. In spite of this, the total seizure burden can be very significant. Neonatal seizures have a focal onset, whereas a generalised onset spike and wave seizure discharge is extremely rare. Neonates can display simultaneous independent focal electrographic seizures (Figure 1). Neonatal status is currently defined as a total seizure time occupying 50% of a recording. Abnormal background activity is associated with an increased risk of seizures^{17,56} and poor neurodevelopmental outcome.

Discharges of less than 10 seconds' duration have been termed BIRDs (brief inter-ictal rhythmic discharges or brief ictal rhythmic discharges) and are of uncertain significance. However, BIRDs have been associated with seizures in the same or subsequent EEG and with poor neurodevelopmental outcome¹⁸.

EEG can provide confirmation that any suspicious phenomena are seizures. However, not all clinically observed seizures are detected by EEG and many neonatal seizures are subclinical (electro-cortical disassociation). Two explanations have been proposed: (1) some seizures may originate at a subcortical level and are not propagated to surface electrodes because of the immature synaptogenesis and cortical projections¹⁹ and (2) some subtle and tonic seizures might not be epileptic but are primitive brain stem and spinal motor phenomena¹⁰.

Cerebral function monitoring

The cerebral function monitor (CFM) has the advantage that it is widely available, and interpretation using pattern recognition can easily be learned. However, short seizures (<30 seconds) cannot be detected, low amplitude or focal seizures are easily missed and movement artefacts are difficult to exclude and may look like seizures²⁰. Thus, in neonates CFM is prone to false-negative and false-positive errors. In particular, non-experts are prone to false negative errors and the inter-observer agreement is low^{21,22,57}.

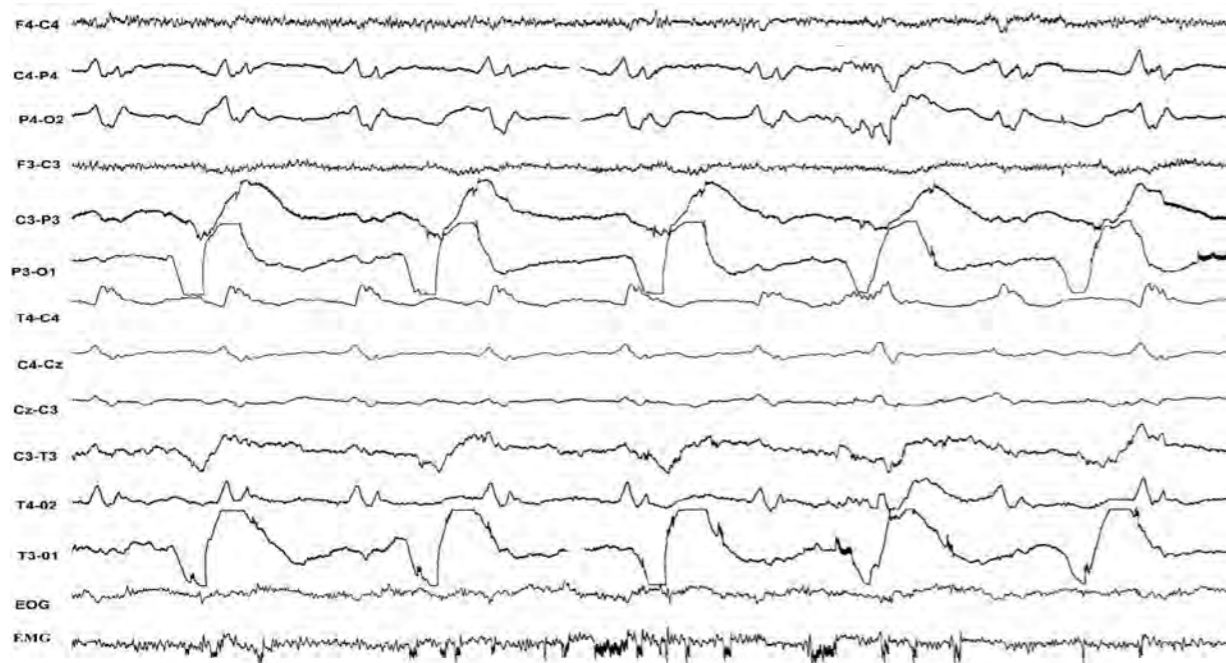


Figure 1. Characteristic features of neonatal seizures: two simultaneous, but quite different seizure pattern discharges over right and left hemispheres. There were no obvious clinical manifestations (an example of electro-clinical dissociation).

Epileptic syndromes

Benign idiopathic neonatal convulsions (fifth-day fits)

Benign idiopathic neonatal convulsions occur around the fifth day of life (day 1 to day 7, with 90% between day 4 and 6) in otherwise healthy neonates. At present the aetiology is unknown. Seizures are clonic, mostly partial and/or apnoeic²³. The inter-ictal EEG shows 'théta pointu alternant' in 60%, in the remaining neonates the background activity is either discontinuous, with focal or multifocal abnormalities, or normal. Ictal recordings show unilateral or generalised rhythmic spikes or slow-waves. Treatment may not be necessary, but the diagnosis is one of exclusion. Seizures usually resolve within days. The outcome is good, but increased risk of minor neurological impairment has been reported^{24,25}.

Benign familiar neonatal convulsions

Benign familiar neonatal convulsions constitute a rare disorder with autosomal dominant inheritance (mutations in the voltage-gated potassium channel genes: most cases 20q13.3, few families 8q24). Seizures occur mostly on the second or third day of life in otherwise healthy neonates and tend to persist longer than in benign idiopathic neonatal convulsions. They are mainly clonic, sometimes with apnoeic spells; tonic seizures have rarely been described. The background activity is normal with no specific pattern. Therapy is controversial and seizures usually resolve within weeks. The outcome is favourable, but secondary epilepsy may occur²³.

Early myoclonic encephalopathy

Early myoclonic encephalopathy²⁶ is a syndrome often associated with inborn errors of metabolism, but cerebral malformations have also been reported. Onset is nearly always in the first month of life and ictal manifestations are as follows: (1) partial or fragmented myoclonus; (2) massive myoclonias; (3) partial motor seizures; (4) tonic spasms. Background activity is abnormal consisting of complex bursts of spikes and sharp waves lasting for 1–5 seconds alternating with flat periods

of 3–10 seconds in both waking and sleep. The EEG later evolves towards atypical hypsarrhythmia. Seizures are resistant to treatment, though ACTH may have some temporary effect. All infants are severely neurologically abnormal and half of them die before the age of one year.

Early infantile epileptic encephalopathy with burst-suppression pattern (Ohtahara syndrome)

Age of onset is in the first three months of life with frequent tonic spasms (100–300 per day), often in clusters²⁷. Partial motor seizures may also occur. The EEG is characterised by true burst-suppression pattern, both in sleep and waking. It may be asymmetric. During seizures desynchronisation is seen. This syndrome is usually associated with cerebral malformations, e.g. Aicardi syndrome or porencephaly. Seizures are resistant to treatment, though ACTH may have some temporary effect. The prognosis is serious, but may be somewhat better than for early myoclonic encephalopathy. Evolution into infantile spasms is common.

Both EME and Ohtahara syndrome have clinically and electrographically distinct features. However, there are also similarities, which have prompted some to suggest that they are not two syndromes, but rather part of a spectrum of a single disorder²⁶.

Inborn errors of metabolism presenting with neonatal seizures

There are also a group of metabolic disturbances, which may present as otherwise medically intractable seizures:^{58,59}

- Pyridoxine dependency
- Pyridoxal phosphate dependency
- Folinic acid responsive seizures/Serine deficiency
- Glucose transporter 1 deficiency
- Biotinidase deficiency
- Creatine deficiency (GAMT)
- Untreated phenylketonuria

Neonates with persistent seizures or suggestive EEG background abnormalities should all undergo a therapeutic trial with pyridoxine, pyridoxal-5-phosphate, and folinic acid⁵⁸. Unexplained and persistent hypoglycaemia should be thoroughly investigated (lactate, ammonia, amino acids, urine organic acids, urine ketones, insulin, cortisol, free fatty acids, and B-hydroxybutyrate).

Glycine encephalopathy (neonatal non-ketotic hyperglycinaemia)

This inborn error of metabolism usually presents as an early myoclonic encephalopathy (see above) with seizures (myoclonus elicited by tactile and painful stimuli) on the second or third day of life. Associated respiratory distress syndrome, with periodic respiration, and coma are found. The EEG shows unusual periodic discharges on a near silent background²⁸.

Glucose transporter type 1 syndrome

Glucose transporter deficiency is a cause of seizures starting in the first three months of life, with mixed seizure types, postnatal microcephaly and encephalopathy later in the first year of life²⁹.

Pyridoxine dependency

Pyridoxine dependent seizures are a rare but treatable subgroup of neonatal seizures, which can begin in intrauterine life³⁰. Seizures of multiple types usually begin shortly after birth and are resistant to conventional antiepileptic drugs (AEDs). There may be encephalopathy and/or structural brain abnormalities. The EEG shows burst-suppression pattern, which may be interrupted by focal seizures or other generalised epileptiform activity. Pyridoxine/pyridoxine-5-phosphate is required for the synthesis of several neurotransmitters, including gamma amino butyric acid

(GABA), monoamines and others. Mutations in the ALDH7A1 gene, which encodes antiquitin, were recently described in some children with pyridoxine-dependent seizures and linkage to 5q31 in some affected families. Pilocarpic acid in plasma and cerebrospinal fluid is considered a possible metabolic marker for this disorder³⁰. When pyridoxine dependency is suspected, 100–200 mg of pyridoxine should be given intravenously under EEG control. The seizures will abruptly stop (within minutes) and the EEG will normalise during the next few hours. Acute suppression of EEG activity occurs occasionally and may be associated with acute cardiovascular collapse. A subgroup of affected babies responds only to very high doses given for two weeks. A closely related disorder with a similar clinical picture has now been identified as pyridoxal-5-phosphate dependent seizure.

Folinic acid responsive seizures are a rare cause of neonatal seizures with clinically similar features to pyridoxine dependent seizures³⁰.

Seizures in hypoxic-ischaemic encephalopathy

Hypoxic ischaemic encephalopathy (HIE) is a common and important cause of seizure in neonates born at term. The characteristic time of onset of seizures in HIE is 8–36 hours after birth. Seizures occurring before that are usually ‘clinical only’ and are due to an abnormal increase in tone. This appears to be similar to animal studies in which the EEG activity in lambs with an intrapartum insult is at first depressed, and then evolves to show seizure activity about eight hours after birth³¹. An EEG obtained shortly after birth in which electrographic seizure activity was already manifest, would strongly suggest an insult over eight hours before delivery. Early background EEG activity is a relatively reliable prognostic indicator for outcome^{32,33}.

Treatment

Phenobarbitone remains in Europe and overseas the drug of choice in the treatment of neonates^{60,61}. The initial dose is 20 mg/kg in unventilated babies and 30 mg/kg in those who are ventilator-dependent (Table 3), aiming to achieve a serum level of 90–180 µmol/L. Phenobarbitone achieves clinical control in only 30–40% of cases³⁴; some claim better clinical control with doses of up to 40 mg/kg and serum levels above 180 µmol/L³⁵. There is, however, evidence that phenobarbitone increases the electroclinical dissociation: while the number of electroclinical seizures decreases, the number of electrographic seizures increases^{36,37}. It has been suggested that this is due to a time difference of the GABA switch which is earlier in thalamic compared to neocortical neurons³⁸.

Phenytoin and clonazepam are used as second-line AEDs. Phenytoin can cause significant myocardial depression and should be avoided in babies requiring inotropic support. Clonazepam may achieve better EEG control. Midazolam^{39,63} has a shorter half-life than clonazepam and does not accumulate, and it avoids the side effect of increased oropharyngeal secretions. Others have reported success with lignocaine^{40,63,64}: between 70% and 92% of newborns responded to lignocaine as second-line AED^{41–43}. However, all these studies were uncontrolled, apart from one with small numbers⁴². Lignocaine has a narrow therapeutic range and can induce seizures in high doses. There is little experience with carbamazepine, vigabatrin and lamotrigine in the neonatal period. Consider a trial of pyridoxine, pyridoxal-5-phosphate and folinic acid.

A Cochrane report has reviewed the treatment of neonatal seizures⁴⁴. Only two randomised controlled studies were identified using adequate methodology^{34,42}, both indicating that current first-line treatment was only effective in about 40–50% of babies. A recent WHO review on neonatal seizures came to a similar conclusion⁴⁵. This situation has led to high usage of off-label drugs in this vulnerable age group⁴⁶, which is associated with a high risk of adverse events⁶⁵. Only recently newer AEDs have been developed and evaluated specifically for the use in the neonatal period⁶⁵. For reviews on AED treatment of neonatal seizures see van Rooij *et al* and Pressler and Mangum^{64,66}.

Table 3. Antiepileptic drug dose in the newborn.

Drug	Initial dose	Route	Maintenance	Route	Therapeutic level
Phenobarbitone	20-40 mg/kg	iv	3-5 mg/kg	iv/im/o	90-180 mmol/L
Phenytoin	15-20 mg/kg	iv/20 min	3-5 mg/kg	iv/o	40-80 mmol/L
Lorazepam	0.05-0.1 mg/kg	iv	every 8-12 hrs	iv	
Diazepam	0.2-0.5 mg/kg	iv	every 6-8 hrs	iv	
Clonazepam	0.1 mg/kg	iv/30 min			30-100 mg/L
Midazolam	0.1-0.2 mg/kg	iv	0.1-0.3 mg/kg/h	iv	
Lignocaine	2 mg/kg	iv	1-6 mg/kg/h	iv	3-6 mg/l
Valproate	10-20 mg/kg	iv/o	20 mg/kg	o	275-350 mmol/L
Paraldehyde	0.1-0.2 ml/kg	pr			
Pyridoxine (B6)	50-100 mg	iv	100 mg every 10 min (up to 500 mg)		

Prognosis

This is mainly determined by the aetiology^{67,68}. The prognosis after hypocalcaemic seizures and in familial neonatal seizures is excellent. Symptomatic hypoglycaemia and meningitis have a 50% chance of sequelae in the survivors⁴⁷. In hypoxic ischaemic encephalopathy the prognosis depends very much on the grade (overall 30–50% normal), while CNS malformations are generally associated with poor outcome. Very low birthweight infants with clinical seizures have a higher incidence of impairment than preterm infants without seizures⁴⁸.

There is increasing evidence that neonatal seizures have an adverse effect on neurodevelopmental outcome, and predispose to cognitive, behavioural, or epileptic complications in later life. In animal studies, seizures impair neurogenesis and derange neuronal structure, function and connectivity leading to permanent effects on seizure susceptibility, learning and memory⁴⁹. Recent work has also shown how even a single seizure in the neonatal period may lead to long-term neurodevelopmental consequences⁵⁰.

Undetected and untreated seizure activity increases the insult to the neonatal brain⁵¹. Seizures add to the hypoxic-ischaemic insult in newborn animals, and the same may be true for babies^{1,52}.

More recently a clear association between the number of electrographic seizures and subsequent mortality and morbidity has been shown¹⁴, illustrating the need for EEG monitoring in neonatal seizures.

However, there is increasing concern about the potentially adverse effects of AEDs on the developing nervous system. In animal models, phenobarbitone has been shown to cause additional brain damage by increasing neuronal death (apoptosis)^{53,54}. Better treatments for neonatal seizures have been identified as a high priority for research by several international expert groups, with emphasis on innovative strategies targeted specifically to the needs of babies with the ultimate aim to improve long-term outcome.

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CHAPTER 7

Severe paediatric epilepsy syndromesCOLIN D. FERRIE¹ & J HELEN CROSS²¹Leeds General Infirmary, Leeds. ²UCL Great Ormond Street Institute of Child Health, London.

Introduction

Most children who develop an epileptic seizure disorder do well. As many as 60–70% can expect to eventually become seizure free either through medication or spontaneous remission. This chapter concerns those who do not. It deals with those epilepsies which can reasonably be predicted to follow a more complex course, rather than with those which are usually relatively mild, but which can, on occasions, prove more difficult.

The term ‘severe paediatric epilepsy syndrome’ does not have a precise meaning. Other terms with which it overlaps include:

- Refractory epilepsy
- Drug-resistant epilepsy
- Complex epilepsy.

In the ILAE’s 2001 Diagnostic Scheme, the term ‘epileptic encephalopathy’ was introduced and defined as:

‘A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function’.

In the 2010 reorganisation¹, epileptic encephalopathy was recognised as a concept that could be applied to any form of epilepsy but there was recognition that children with some epilepsy syndromes were more at risk than others, and it is these epilepsies that may previously been referred to as epileptic encephalopathies. Most of the conditions discussed in this chapter are, however, developmental epileptic encephalopathies (see Chapter 2). Hence they are characterised not only by pharmaco-resistant epileptic seizures but also with an expectation that children will develop other problems, including learning difficulties, behavioural problems (including autistic behaviours) and sometimes physical problems such as ataxia that may be in part, but not totally related to, the epilepsy itself. Some of the disorders discussed, such as Ohtahara and West syndromes, always behave as epileptic encephalopathies. Others, such as Dravet and Lennox Gastaut syndromes, usually do. While others, such as Doose syndrome, often do but quite frequently do not. Furthermore, we need to recognise that many of these syndromes are not limited to childhood; they may start in childhood, but many grow and survive into adulthood. Many aspects of management pertain to care throughout the lifespan.

The epileptic encephalopathies are not neurodegenerative disorders in the usual meaning of that term. Therefore, we will not be considering conditions such as the cerebral lipofuscinoses (‘Batten Disease’).

What makes an epilepsy severe?

We do not know the answer to this question. Almost certainly it has something to do with aetiology. Until recently, 'idiopathic' was often equated with 'mild' or 'benign' and 'symptomatic' with 'severe'. Also, it was felt likely that epilepsies caused by ion channel disorders would be relatively mild. It is now clear that these are huge oversimplifications. Doose syndrome is considered a genetic generalised epilepsy but it often acts as an epileptic encephalopathy. Children with congenital hemiplegia, caused by middle cerebral artery infarcts, may develop a severe epilepsy but the epilepsy may be self-limiting. Dravet syndrome (one of the most severe of all childhood onset epilepsies) is a channelopathy. It is a consequence of the increasing understanding of underlying aetiologies to the syndromes, and the recognition that comorbidities are integral to the disease entity that the International League Against Epilepsy proposed the new classification framework in 2017, allowing the epilepsies to be described at many levels (see Chapter 2).

Severe epilepsy syndromes of the neonatal period

There are two well described developmental epileptic encephalopathies in this age group. They share some common features.

Ohtahara syndrome (also known as early infantile epileptic encephalopathy)

This is a rare epilepsy syndrome usually presenting in the first few days or weeks of life, but sometimes as late as three months of age. Clinically it is characterised by the occurrence of tonic seizures which can be generalised and symmetrical or lateralised. These tend to be very frequent (often hundreds a day), occur both during awake and sleep and can be single or occur in clusters (similar to infantile spasms). Other seizure types include focal motor seizures and hemi- or generalised tonic-clonic seizures. Myoclonic seizures are not characteristic. The EEG shows a burst-suppression pattern both during awake and sleep (Figure 1). Bursts, usually lasting 2-6 seconds, consist of high amplitude slow waves intermixed with spikes. These alternate with periods of suppression, usually lasting for 3-5 seconds, during which the EEG is flat or nearly flat. Tonic seizures can occur during the bursts or can be associated with periods of desynchronisation or 'accentuation' of the burst-suppression pattern.

Ohtahara syndrome is commonly caused by severe cerebral malformations, such as hemimegalencephaly, diffuse migrational disorders, porencephaly, Aicardi syndrome, etc. The prognosis is very poor. Half of infants affected are said to die within weeks or months of its onset. The remainder are left with severe learning difficulties and often with motor impairments (cerebral palsy). Survivors often show an evolution to West syndrome and this may subsequently evolve to Lennox-Gastaut syndrome. This observation led to the concept of the age-related encephalopathies - differing presentations of electroclinical syndromes with the same cause presenting at different ages.

Treatment with antiepileptic drugs (AEDs) is usually ineffective. ACTH has been used, usually without effect.

Early myoclonic encephalopathy

This is also a rare neonatal epilepsy syndrome often presenting very shortly after birth and nearly always within the first few weeks of life. It is characterised by erratic or fragmentary myoclonus consisting of myoclonias affecting the face and limbs which shift from one part of the body in a random and asynchronous manner. They may be single or repetitive and are usually very frequent, if not near continuous. Massive axial myoclonic jerks may also occur. Other seizure types seen include: focal seizures, often subtle and manifested with, for example, eye deviations or autonomic symptoms; tonic seizures; and epileptic spasms (usually later in the evolution of the disorder). The

EEG shows a burst-suppression pattern (Figure 1), often more apparent in sleep than when awake. The myoclonias do not usually have an EEG correlate.

Early myoclonic encephalopathy is often caused by inborn errors of metabolism, such as amino and organic acidurias, disorders of purine metabolism and peroxisomal disorders. Detailed metabolic studies are mandatory. These should include CSF studies for glycine to exclude non-ketotic hyperglycinaemia. Not surprisingly, autosomal recessive inheritance is often apparent. Structural brain defects, except for the development of diffuse atrophy, are not expected. Unless a treatable metabolic disorder is found no effective treatment exists. There is a very high mortality in the early weeks and months of life and survivors are left with severe physical and mental impairments.

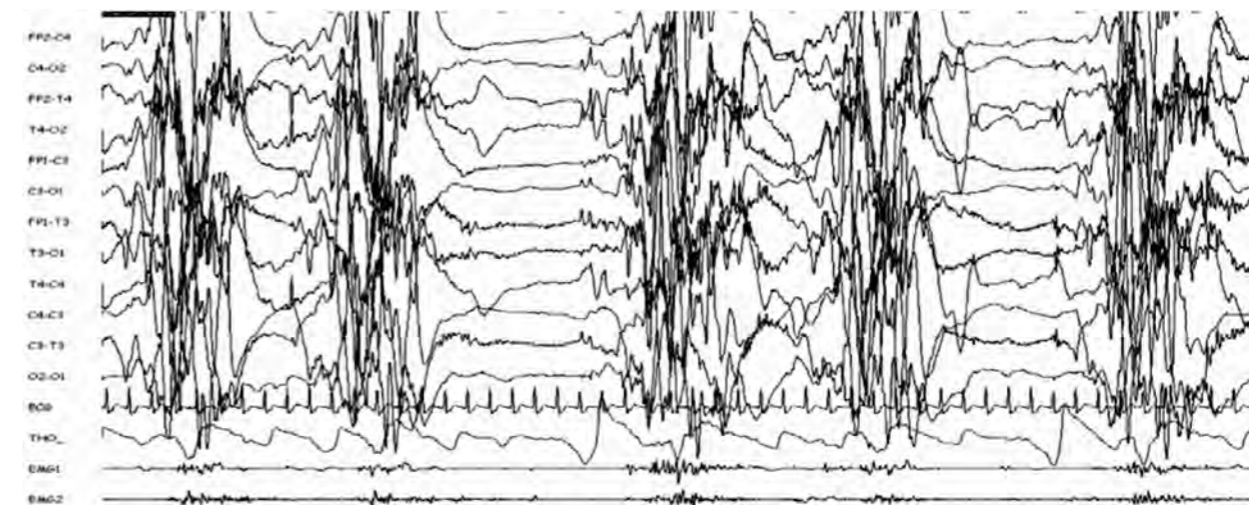


Figure 1. Burst-suppression (15 mm/sec). This example is from a 15-day-old infant with early myoclonic encephalopathy.

Severe epilepsy syndromes of infancy

West syndrome

West syndrome comprises a triad of epileptic spasms, developmental plateau and hypsarrhythmia. It usually starts between three and 12 months of age, with a peak at five months. It has an incidence of 3-5 per 10,000 and it is more common in boys.

The defining seizure type is epileptic spasms. This term is now preferred to infantile spasms, recognising the fact that the seizure type can occur in older children. They consist of sudden, brief contractions of axial and limb muscles lasting longer than myoclonic seizures (i.e. longer than 100 milliseconds) and shorter than tonic seizures (i.e. shorter than a second - although many would say shorter than two seconds). Characteristically they occur in clusters, which may include tens or even hundreds of individual spasms. Spasms may be flexor, extensor or mixed flexor-extensor. The type does not appear to be important in terms of aetiology or prognosis. They are usually symmetrical. However, asymmetrical spasms do occur and often indicate focal structural brain pathology. Indeed, a cluster of spasms may be preceded by or be followed by a focal seizure. Spasms usually occur on arousal or when alert. Exceptionally they occur during sleep. Loud noises, tactile stimuli and feeding may all precipitate spasms. Early in the course of the condition spasms may be very subtle and infrequent (sometimes manifested with head nods) but tend to build up both in intensity and frequency such that they eventually become obvious.

Prior to the onset of spasms development may have been normal or delayed, reflecting the underlying aetiology. Where development has been normal parents often first notice a period of social disengagement, particularly for visual stimuli. Developmental deterioration during the period of active spasms is usual but not universal. Most children who have had spasms will eventually have severe learning difficulties, but up to 15% will show normal or near normal development.

Hypsarrhythmia is the EEG pattern most commonly seen in children with West syndrome (Figure 2). However, up to one-third have other patterns. It comprises a chaotic mix of asynchronous high amplitude slow waves with intermixed sharp waves and spikes. So-called atypical or modified hypsarrhythmia includes cases with asymmetries, persistent foci, some preservation of background rhythms and a degree of synchrony. Some of these, particularly the first two, are associated with structural brain aetiologies. During non-REM sleep a degree of synchronisation is common and there may be preserved sleep elements. The EEG is usually normal in REM sleep. Particularly early in the disorder, the awake EEG may be normal while the sleep EEG is abnormal. The ictal EEG, that is the EEG associated with spasms, is very variable, with at least 11 patterns being described. However, most commonly it shows a brief period consisting of a generalised high voltage slow wave, episodic, low amplitude fast activity and then attenuation or flattening of the EEG (electrodecremental response).

As with many early onset epilepsy syndromes, the electroclinical pattern seen is common to many underlying aetiologies; West syndrome is an age dependent encephalopathy. At least 85% of cases are associated with an underlying aetiology. (Table 1). The single commonest cause is tuberous sclerosis. An increasing number where an aetiology was not previously apparent have now been found to be genetic in origin, e.g. CDKL5 in girls, STXBP1. Many evolve into a further age dependent encephalopathy Lennox Gastaut Syndrome.

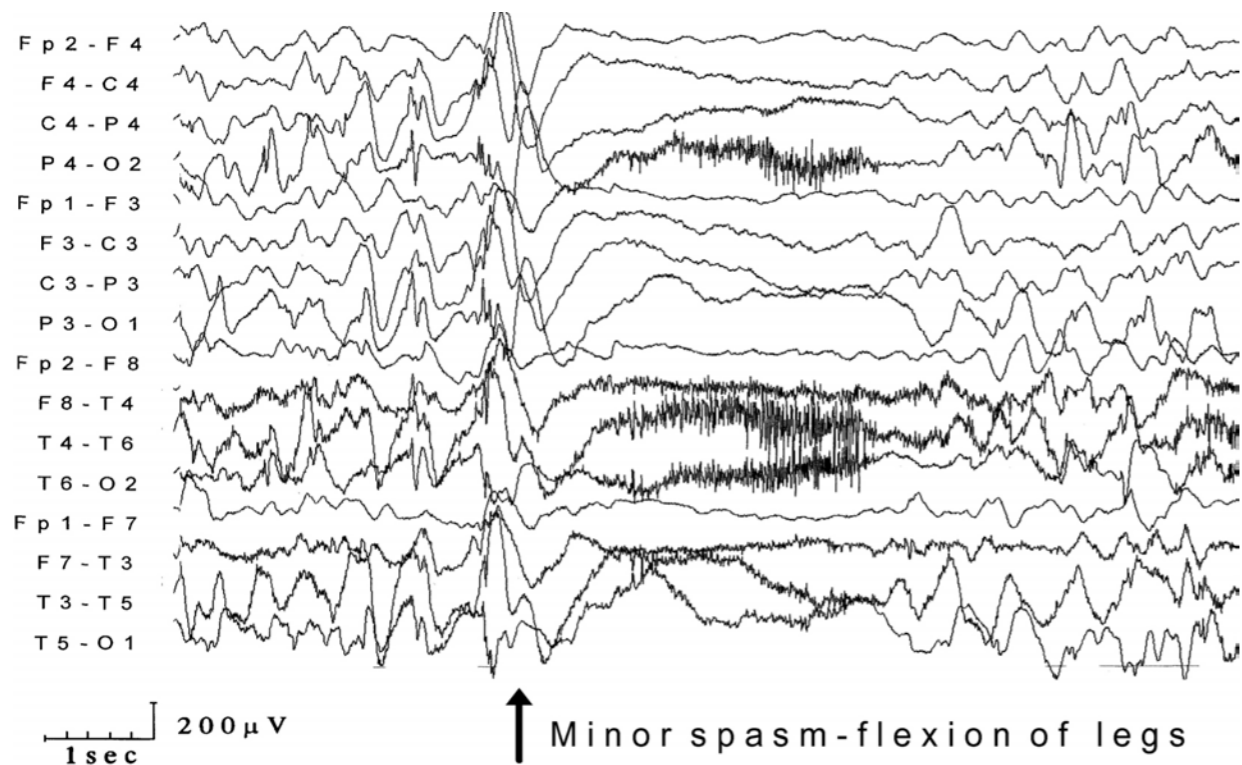


Figure 2. EEG from a child with Down syndrome and epileptic spasms. The initial EEG shows symmetrical hypsarrhythmia. The spasm coincides with a large amplitude slow wave followed by an electrodecremental response.

Table 1. Main causes of West syndrome. Most can also cause the Lennox-Gastaut syndrome.

	Disease category	Examples
Structural	<i>Neurocutaneous syndromes</i>	Tuberous sclerosis Sturge-Weber syndrome Incontinentia pigmenti
	<i>Malformations of cortical development</i>	Aicardi syndrome Lissencephaly Pachygyria Polymicrogyria Laminar heterotopias Hemimegalencephaly Schizencephaly Holoprosencephaly
	<i>Hypoxic-ischaemic insults</i>	Neonatal HIE
	<i>Congenital infections</i>	Cytomegalovirus Rubella Toxoplasma
	<i>Perinatal trauma</i>	Intracranial haemorrhage Neonatal cerebrovascular event
Genetic	<i>Severe perinatal/postnatal infections</i>	Meningitis Encephalitis
	<i>Chromosomal</i>	Down syndrome Fragile X syndrome X-linked infantile spasms
Metabolic	<i>Single gene disorders</i>	Miller-Dieker syndrome CDKL5 deficiency disorder STXBP1 mutation
		Pyridoxine dependency Amino and organic acidopathies Mitochondrial disorders

West syndrome is usually easily recognised but can be confused with a number of epileptic and non-epileptic disorders, including: benign (non-epileptic) myoclonus of infancy, benign neonatal sleep myoclonus, Sandifer's syndrome and colic.

There are many treatment strategies for West syndrome. Steroids have long been recognised to be effective and vigabatrin particularly effective for spasms due to tuberous sclerosis. A recent UK multicentre trial (UKISS) comparing steroid and vigabatrin treatment for spasms not due to tuberous sclerosis found evidence in favour of the former. The subsequent International Collaborative Infantile Spasm Study (ICISS) published recently, further evaluated steroids with vigabatrin vs steroids alone and showed greater short term efficacy with combination therapy. Further evaluation at 18m, however, did not demonstrate any difference in neurodevelopment. The subsequent antiepileptic treatment should either of these fails, is less clear. Conventional AEDs may have a role and in France high-dose sodium valproate has been used first line. Pyridoxine is popular, particularly in Japan. Surgery should be considered early in cases due to focal brain pathology and children with such referred immediately for assessment in an epilepsy surgery centre.

The prognosis is generally, but not universally, poor: 15–30% may become seizure free and develop normally or near normally. However, around 60% are left with intractable seizures (often Lennox-Gastaut syndrome) and two-thirds have severe learning difficulties and/or behavioural problems.

Dravet syndrome

This epilepsy syndrome is increasingly recognised. It is more common in boys. It begins in the first year of life and affected children are previously normal. The first seizure is usually febrile. There may be nothing remarkable about the seizure but characteristically it is complex, being prolonged and/or focal. Febrile status is common. In addition, the provoking fever is often relatively mild. Indeed in some cases the child may simply be unwell without clear evidence of a fever. The child recovers as expected but further similar seizures usually occur, often becoming more and more frequent with time. Some are provoked by non-febrile illnesses, immunisations, hot baths and even hot weather. During this stage of the condition, development continues normally. A second stage then ensues, usually in the second or third year of life, with the development of multiple seizure types, often including myoclonic seizures, febrile and non-febrile convulsive seizures (tonic-clonic, clonic or hemiconvulsions), atypical absences and focal seizures. Episodes of convulsive and non-convulsive status epilepticus may occur. As well as temperature provoking seizures, some patients are photosensitive. During this stage of the disease development stagnates, with little in the way of cognitive progress so many have severe learning difficulties in later childhood. In late childhood a final stage ensues during which seizures tend to continue but are less frequent.

At presentation the EEG in Dravet syndrome is usually normal, except that about one-fifth of subjects show very early photosensitivity. With the onset of the further seizure types the EEG begins to slow and becomes dominated by diffuse theta and delta. Paroxysmal abnormalities of polyspike and/or spikes and slow waves usually become frequent occurring in brief bursts, which are often asymmetrical.

More than 80% are associated with a mutation in the sodium channel gene, SCN1A. This also in the majority is de novo, although in around 10% a parent may be mosaic with no symptoms. The latter may lead to recurrence in a subsequent sibling, and therefore genetic counselling is imperative.

Response to AEDs is poor, although temporarily good results can be obtained from a number of agents. Carbamazepine, phenytoin and lamotrigine may exacerbate seizures and should be avoided. Several agents have now been demonstrated through randomised controlled trials to be useful. Stiripentol in conjunction with sodium valproate and/or clobazam has been shown to be beneficial and is currently standard care. Cannabidiol and particularly fenfluramine have also been shown to be effective over placebo, and are currently undergoing regulatory approval, Topiramate, perampanel and the ketogenic diet may also be useful.

Epilepsy of Infancy with migrating focal seizures (EIMFS) (also called malignant migrating partial seizures in infancy)

This rare syndrome starts any time between birth and about seven months in previously normal children. It is characterised by focal seizures with motor and prominent autonomic symptoms evolving to bilateral convulsive seizures. Seizures vary in their intensity and duration; episodes of status are common. The seizures tend to increase in frequency, becoming virtually continuous. EEG background is slow with varying side emphasis and multifocal spikes develop. Ictal discharges involve multiple independent sites, moving from one cortical area to another during the same seizure. Investigations, except EEG are normal. It is likely to be genetic in origin; a recent study suggested up to 50% may be due to a mutation in the KCNT1 gene. Response to treatment is poor and there is a high mortality.

Severe epilepsy syndromes of childhood

The following epilepsy syndromes in childhood are often severe, constituting epileptic encephalopathies: Lennox-Gastaut syndrome; Doose syndrome; Landau-Kleffner syndrome and the related disorder of epilepsy with continuous spike and waves during slow-wave sleep; and myoclonic absence epilepsy. Note that the propensity of these syndromes to act as epileptic encephalopathies varies: Landau-Kleffner syndrome always does so whilst Doose syndrome, which is classified as a genetic generalised epilepsy, sometimes does but often does not.

Lennox-Gastaut syndrome

Probably no syndrome diagnosis is more abused and misunderstood than Lennox-Gastaut syndrome (LGS). Some authorities classify virtually all drug-resistant epilepsies characterised by multiple seizure types as LGS. Used in this way, the diagnosis is of little use in helping management. The alternative, much favoured in Europe and increasingly in the UK, is to use a narrower definition of the syndrome. This approach will be used here. LGS usually begins between three and five years of age, but can start as early as one year or as late as adolescence. Its incidence is said to be 2.8 per 10,000 live births but because of its intractable nature its prevalence in children with seizures may be up to 5%. It is characterised by seizures of multiple, mainly generalised, type and learning difficulties.

The three most characteristic seizure types are tonic (particularly axial tonic seizures), atonic and atypical absence seizures. However, other seizure types may occur, including GTCS and focal seizures. Myoclonic seizures are not usually prominent, although they can occur. Tonic, atonic and to a lesser extent, myoclonic seizures frequently cause ‘drop’ seizures in LGS. Finally, episodes of non-convulsive status epilepticus are common.

The background EEG in LGS is usually diffusely slow. Two main paroxysmal EEG features help in the diagnosis. These are (Figure 3):

- Slow (<2.5 Hz) spike and wave discharges which are usually generalised and symmetrical but can be asymmetrical, unilateral or even regional. They can be inter-ictal or ictal. If the latter they can be associated with atypical absences or atonic seizures.
- Fast rhythms or rhythmic rapid spikes at frequencies of 10–20 Hz which are usually seen in slow wave sleep. These may accompany tonic seizures.

The causes of LGS remain unclear but are similar to those seen in West syndrome (Table 1), from which LGS sometimes evolves. Two-thirds to three-quarters of children with LGS have developmental problems prior to onset of seizures. This reflects the diverse aetiologies associated with LGS. With the onset of seizures development stagnates and, at times of particularly frequent seizures, may regress. Nearly but not all children with LGS eventually have learning difficulties, usually severe, and behavioural problems are also very frequent. With increasing age some children become seizure free but many continue to have the phenotype of LGS into adult life or develop a rather non-specific epilepsy with less frequent convulsive and non-convulsive seizures. Features which suggest a better prognosis include those where a definitive cause is not found, more frequent myoclonic seizures, EEGs which feature some fast spike and/or polyspike and wave discharges, older age of onset and rapid control of seizures.

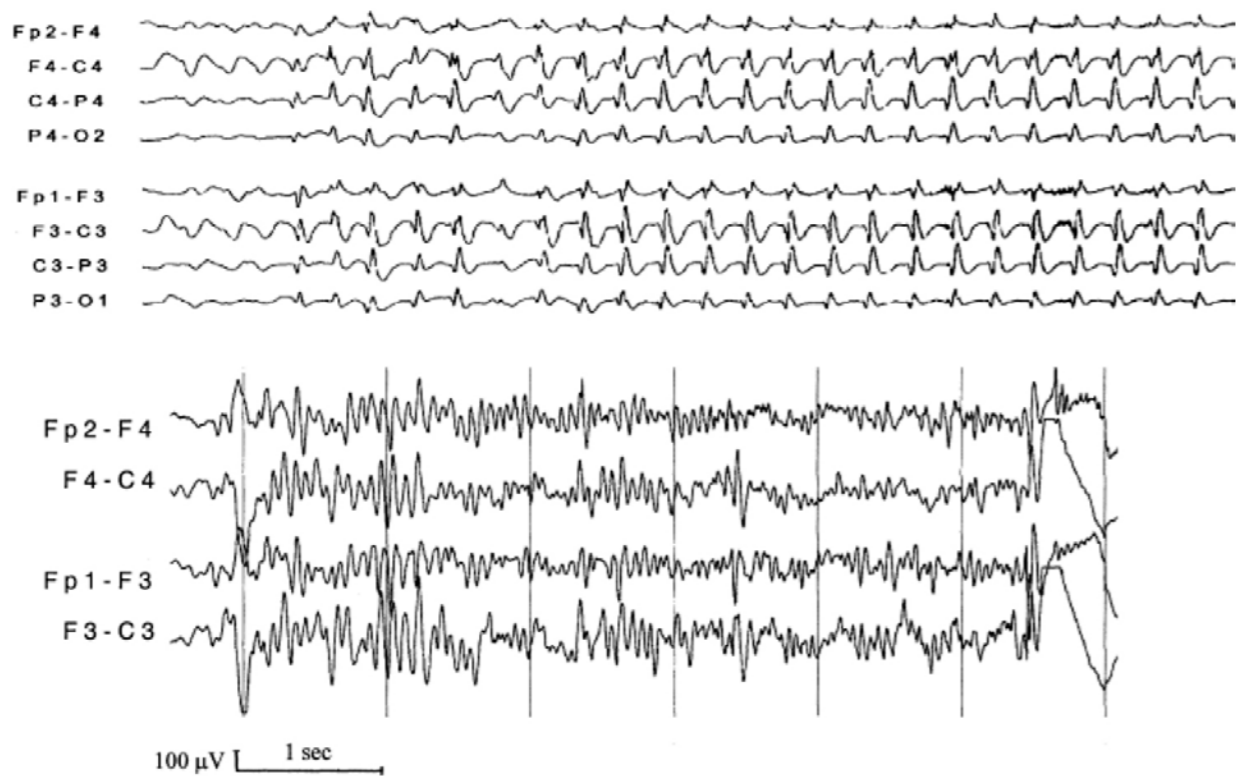


Figure 3. Upper EEG - Slow spike and wave discharge; lower EEG - fast rhythms.

LGS is invariably drug resistant. Although some children will respond to AEDs, albeit often only temporarily. Drugs active against generalised seizures, particularly sodium valproate, are usually utilised first. Benzodiazepines and lamotrigine can also be helpful, although the latter may exacerbate myoclonic seizures. Ethosuximide may help atypical absences. Drugs such as carbamazepine and phenytoin should be used with particular caution as they may exacerbate some seizure types. Felbamate, topiramate, lamotrigine, clobazam, rufinamide and more recently cannabidiol have all been shown in randomised controlled studies to be superior to placebo in LGS and both levetiracetam and zonisamide are also probably appropriate drugs to try. Non drug treatments which can be helpful include the ketogenic diet and vagal nerve stimulation. Very occasionally children develop LGS as a consequence of surgically remediable focal pathology. Callosotomy has an occasional role to play for the treatment of atstatic seizures.

Doose syndrome (also called epilepsy with myoclonic-atonic seizures or epilepsy with myo-atonic seizures)

This syndrome usually starts between two and four years of age but can begin as early as the first year of life or up to mid-childhood. Boys are affected more than girls and development is normal prior to the onset of seizures. It is now considered to be a genetic generalised epilepsy (GGE).

In most children with Doose syndrome the first seizures are febrile or afebrile GTCS. These are then followed by the characteristic seizure, the so-called myo-atonic seizure, which combines a symmetrical myoclonic jerk immediately followed by an atonic seizure - usually causing a drop attack. Children with Doose syndrome may also have independent atonic and myoclonic seizures and brief typical absence seizures. Episodes of non-convulsive status epilepticus lasting hours or days occur in some children. Being a GGE, investigations other than EEG are expected to be normal. Inter-ictal EEG may show rhythmic theta in the parasagittal regions, with frequent clusters

of generalised spike-wave discharges at 2-3 Hz and/or polyspike or polyspike and wave discharges (Figure 4). These patterns may also be ictal.

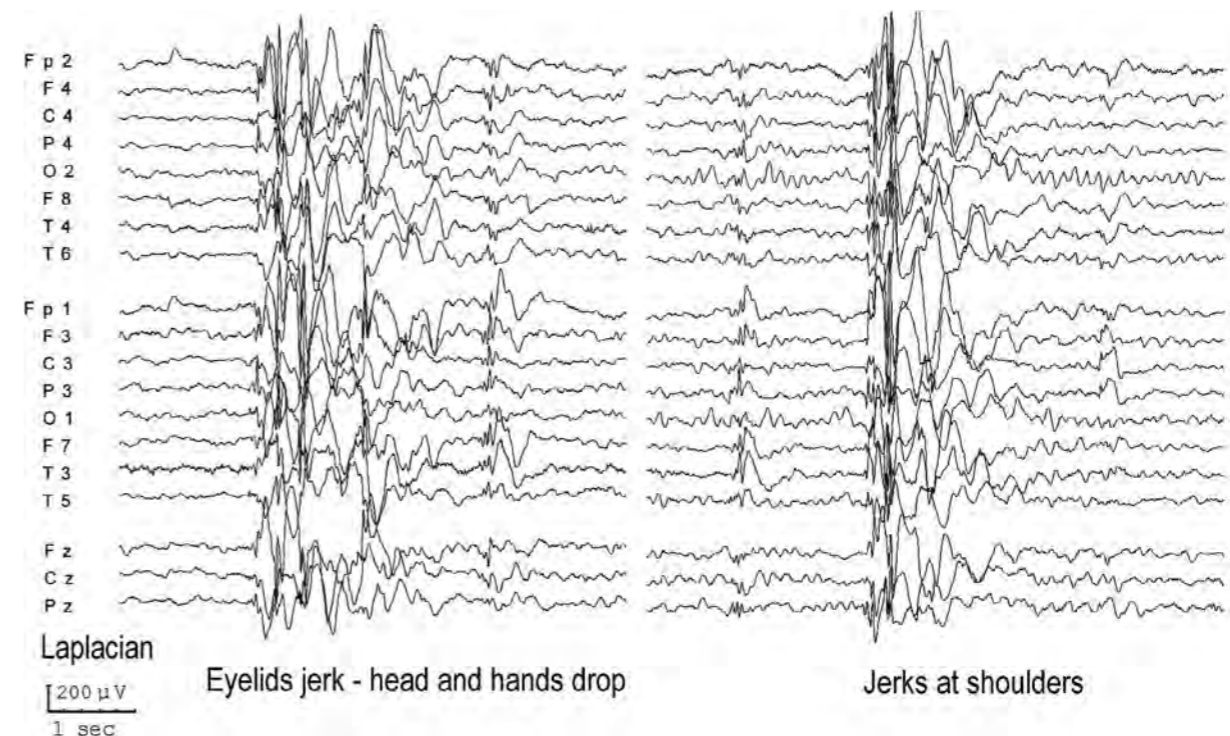


Figure 4. The EEG from a six-year-old boy with Doose syndrome.

The prognosis is variable. Many children (perhaps up to half) with the syndrome become free of the drop attacks, although they may continue to have GTCS, and develop normally or near normally. In others drop attacks may continue for years and learning difficulties become apparent. It is these children with Doose syndrome who appear to have an epileptic encephalopathy.

The response to AEDs varies from complete responses to marked drug resistance. Drugs active against generalised epilepsies should be used. These include sodium valproate, topiramate, levetiracetam and benzodiazepines. Lamotrigine may also be helpful but there is concern that it can exacerbate myoclonic seizures. Drugs mainly active against focal seizures, such as carbamazepine may exacerbate seizures and should be avoided. Doose syndrome often responds very well to the ketogenic diet.

Landau-Kleffner syndrome and ECSWS (or ESES)

Landau-Kleffner syndrome (also called acquired epileptic aphasia) and epilepsy with continuous spike and waves during slow-wave sleep (ECSWS) or epileptic encephalopathy with electrical status epilepticus during slow-wave sleep (ESES) overlap and therefore will be considered together. The Landau-Kleffner syndrome (LKS) usually starts in otherwise normal children between five and seven years of age but can start much earlier or later. It is more common in boys. It consists of a triad of: an acquired language problem; epileptic seizures; and behavioural problems. The language problem is initially auditory verbal agnosia such that the children find difficulty in attributing semantic value to speech. This is often very severe, causing the children to stop responding initially to the spoken word and sometimes to environmental noises as well. They are often suspected of being

deaf. A secondary motor aphasia commonly develops. Epileptic seizures occur in three-quarters of patients with LKS. The seizures can be of different types including GTCS and focal seizures. They are often, but not always, infrequent. The behavioural problems, often severe, include hyperactivity and attention deficits as well as autistic behaviours. The language problems, behavioural problems and seizures often fluctuate in their severity and this may correlate with the EEG findings.

The EEG is characterised by mainly posterior temporal lobe foci of sharp slow-wave complexes that are often multi-focal and bisynchronous. The awake EEG may be normal but non-REM sleep nearly always markedly increases the epileptiform abnormalities, such that they often occupy at least 85% of non-REM sleep. This constitutes electrical status epilepticus during slow wave sleep (ESES). Although ESES is very common in LKS it is not a prerequisite and its presence may vary between EEGs.

Structural imaging in LKS is usually normal. Functional imaging often implicates the superior temporal gyrus, on one side or the other.

The LKS nearly always eventually remits. Occasionally this can be after only a few weeks or months. More often it continues for some years and adults are usually left with persistent language and cognitive problems, although these are often milder than would be anticipated during the active stage of the condition.

Seizures in LKS often respond well to conventional AEDs but often without improvement in language function or behaviour. However, sodium valproate is often used first line and both ethosuximide and benzodiazepines can be helpful. Following acute regression in skills however a course of high dose steroids is appropriate with review of clinical and EEG response. In the absence of a circumscribed lesion there is no place for surgical intervention.

Epilepsy with continuous spike and waves during slow-wave sleep (CSWS) is a related and overlapping epilepsy syndrome which can start from two months to 12 years. Many children are neurodevelopmentally normal prior to the onset of seizure but others have a variety of developmental problems, including cerebral palsy and learning difficulties. The condition usually starts with seizures which are often nocturnal and hemi-convulsive in type. They may be prolonged constituting status epilepticus. A all types of seizures may occur during this stage, except probably tonic seizures. With the increase in seizures neuropsychological regression occurs and may be severe. There may be, in addition, acquired motor deficits such as ataxia, hemiparesis and dyspraxia. An opercular syndrome with drooling, feeding problems and dysarthria can occur.

The EEG hallmark of ECSWS is continuous (i.e. >85%), bilateral and diffuse spike and waves during non-REM sleep (Figure 5).

Many children with CSWS have structural brain abnormalities. In others the condition develops in previously normal children. An association with mutations in the GRIN2A gene has been determined. It is a rare complication of childhood epilepsy with centro-temporal spikes (rolandic epilepsy) and other self-limiting focal epilepsies of childhood. Carbamazepine has been implicated as precipitating it in some cases. Treatment is similar to LKS and, as for LKS, the condition remits, but usually leaving significant neurodevelopmental problems.

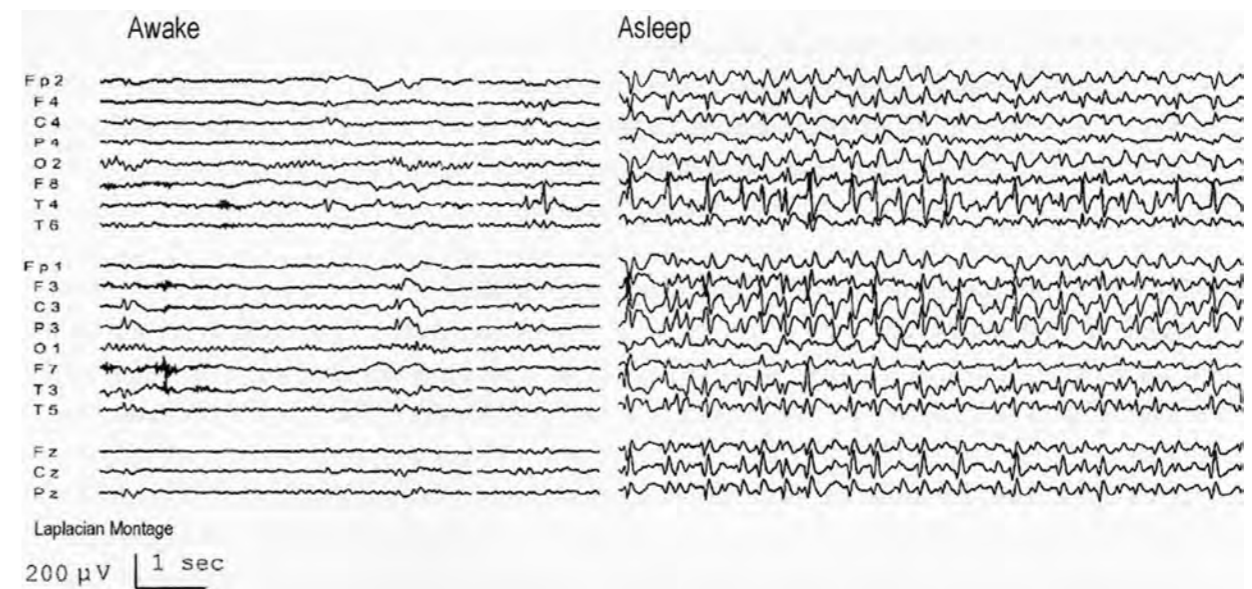


Figure 5. The EEG from a boy with rolandic epilepsy who developed continuous spike and wave during slow-wave sleep.

Epilepsy with myoclonic absences

Epilepsy with myoclonic absences (EMA) is a rare epilepsy syndrome which can start at any time in childhood. The hallmark is myoclonic absence seizures. These are similar to typical absence seizures but with superimposed rhythmic myoclonic jerks mainly of the upper limbs. GTCS and atonic seizures may also occur. The EEG shows a normal background with 3 Hz generalised spike and wave discharges. Simultaneous EMG demonstrates the myoclonic jerks. Marked asymmetries and focal abnormalities may be apparent. Slowing of the background may occur later.

EMA is now classified as a genetic generalised epilepsy (GGE) by the ILAE but most children with myoclonic absences have pre-existing neurodevelopmental problems and a variety of underlying aetiologies, including structural brain defects and chromosomal abnormalities. Impaired cognitive functioning commonly develops even in those children who were normal prior to the onset of the seizures. There is some evidence that successful treatment of the seizures prevents or minimises this. Drugs active against absence seizures in general should be tried and drugs such as carbamazepine mainly active in focal epilepsies should be avoided. Relative seizure resistance is the rule.

Some aetiologies associated with severe childhood epilepsies

Some pathological entities are associated with a high likelihood of intractability. These are not epilepsy syndromes (although some are syndromes as used in the more general sense) but for completeness will be briefly described here.

Rasmussen's encephalitis

This very rare epilepsy usually begins with focal motor seizures, often very localised at least initially. Episodes of focal motor status (epilepsy partialis continuans) is common. Other seizure types, including GTCS, may occur. Over a period which can be only a matter of weeks or else years, a progressive hemiplegia develops along with cognitive decline. Untreated the disease eventually remits but usually leaving a dense motor deficit and severe learning difficulties. Pathologically there are focal perivascular infiltrates characteristic of a viral or autoimmune process: the cause, however,

remains unknown. Early structural scans may be normal or may show focal signal abnormalities. Later hemiatrophy develops. Some reports suggest that bihemispheric involvement may occur but this is controversial. Some response to conventional AEDs may occur, but nearly always this is temporary. Immunological treatments, such as steroids and intravenous immunoglobulin are usually used, sometimes with apparent success. However, most patients eventually require hemispherectomy. Children should be reviewed in a specialised epilepsy surgery unit as timing of surgery will be key to optimise cognitive outcome.

Abnormalities of cortical development

Cortical dysplasias vary greatly in their epileptogenicity. This is perhaps best illustrated by tuberous sclerosis. Some subjects with this live normal lives, others have mild epilepsies and are of normal or near normal intelligence. However, many children with tuberous sclerosis present very early on in life with severe epilepsy, particularly West syndrome, and are devastated by the disorder. Epilepsy surgery may be curative; all children should be referred promptly for evaluation

Hemimegalencephaly is a particularly severe and complex dysplasia affecting one hemisphere (although less severe abnormalities of the 'uninvolved' hemisphere may be present). It often presents with refractory focal seizures in early life. Early hemispherectomy maximises developmental potential.

Glioneuronal tumours (e.g. gangliogliomas, dysembryoplastic neuroepithelial tumours)

These are indolent cortical brain tumours which include both neural and glial elements. Most are temporal in origin but any cortical region can be involved. They may be congenital. They commonly present in childhood or early adult life with focal epilepsy, which has a tendency to be refractory to medical treatment. There is evidence that the early surgical resection not only controls seizures but improves neurodevelopmental outcome in those children who present at an early age with intractable seizures.

Sturge-Weber syndrome

This neurocutaneous disorder features a facial port wine stain with an ipsilateral pial angioma. The clinical consequences are highly variable. However, a minority of affected infants develop: refractory focal seizures, including episodes of potentially devastating status epilepticus; progressive hemiplegia; and progressive cognitive decline. The last two of these appear to be caused by a vascular steal phenomenon related to the pial angioma causing atrophy of the underlying cortex. Surgical treatment with lobar, multilobar or hemispheric resection may halt this progression.

Figures used here have been modified with permission from: *A Clinical Guide to Epileptic Syndromes and their Treatment*, second edition. Springer, London (courtesy of CP Panayiotopoulos)

Further reading

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CHAPTER 8

Febrile seizures – a practical guide

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Introduction

Febrile seizures are a common presentation to the Paediatric Departments. For the parent/carer they can be extremely traumatising to witness and they often have many questions. Will they make a full recovery? Will they have further seizures? Do they have epilepsy?

In terms of outcome, opinions have changed with time. In 1949 Lennox wrote: 'febrile seizures may cause brain pathology as evidenced by transient or permanent neurological deficit'. In contrast, it is now widely accepted that children with febrile seizures have a generally excellent prognosis. Underpinning this change is observations from wider inclusion of population-based studies as oppose to earlier groups studying outcomes of children with associated neurodevelopmental difficulties. In addition, both a clearer definition of febrile seizures excluding those with CNS infection, and extrapolation of data into those with and without meningoencephalitis has further delineated the outcome of children with febrile seizures alone. These more comprehensive studies have shown that febrile seizures are, for the majority, a benign process.

Definitions

Febrile seizures

The American Academy of Pediatrics² has defined a febrile seizure as:

“a seizure accompanied by fever (temperature higher than 38°C by any method), without central nervous system infection, which occurs in infants and children aged 6 months to 5 years”.

Febrile seizures can be sub-classified into simple or complex. The National Institute for Health Care and Excellence (NICE), describe simple and complex febrile seizures as follows³:

Simple febrile seizure

- Isolated
- Generalised convulsion
- Last less than 15 minutes
- Do not recur within 24 hours or within the same febrile illness
- Complete recovery within 1 hour

Complex febrile seizure (one or more of the following):

- Focal seizure (movement limited to one side of the body or one limb)
- Duration of more than 15 minutes
- Recurrence within 24 hours or within the same febrile illness
- Incomplete recovery within 1 hour

Although consensus on these definitions is widely accepted, Hesdorffer *et al* found that the distribution of first febrile seizure duration was best modelled by assuming two populations and their data suggested that ten minutes should be the upper limit for a simple febrile seizure⁴.

Febrile status epilepticus

Defined as a febrile seizure lasting 30 minutes or more or a series of febrile seizures without full return to consciousness during that period^{5,6}.

Epidemiology

Overall rates

Between 2 and 5% of all children have one or more febrile seizures by the age of five years. Boys have a slightly higher risk with a reported male to female ratio of 1.6:1⁷. Racial and geographical differences have also been observed which are likely a reflection of the increasing identification of genetic susceptibility. In America, Nelson and Ellenberg report a prevalence rate of 3.5% in Caucasian children compared to 4.2% in black children⁸, whilst higher prevalence rates of 8.9% by three years of age have been reported in Tokyo⁹.

Age

The age of onset of febrile seizures (as per the accepted definition) is usually between 6 months and 5 years⁷, but there are patients who present out with this age range with onset reported to vary between two months of age and seven years nine months¹⁰. A peak incidence is reported between 12 and 18 months of age⁸.

Aetiology

Genetic factors

There is an expanding literature on the genetics of febrile seizures. Population-based studies suggest that family history is important and that febrile seizures and epilepsy each provide an independent contribution to the familial risk of febrile seizures^{11,12}. Forsgren concluded that multifactorial inheritance was most likely¹³. Family studies have shown that simple febrile seizures may also be inherited as an autosomal dominant trait with high penetrance¹⁴ and show an occurrence rate ranging from 10% to 46% in children with a positive family history of febrile seizures¹⁵. It seems clear that febrile seizures make up an extremely heterogeneous group for which there is no single mode of inheritance.

Causative genes have not been identified in most patients with febrile seizures; however population-based studies have shown at least one positive association with febrile seizures for 14 of 41 investigated genes¹⁵. Mutations in the voltage-gated sodium channel alpha-1, alpha-2 and beta-1 subunit genes (SCN1A, SCN2A and SCN1B) and the GABA(A) receptor gamma-2 subunit gene (GABRG2) have been identified in families with 'generalised epilepsy with febrile seizures plus' (GEFS+)¹⁶. Patients with GEFS+ can have febrile seizures followed by afebrile (often generalised) seizures¹⁷. There is evidence that the well-recognised syndrome of epilepsy, hippocampal sclerosis and febrile seizures can be associated with common genetic variation around the SCN1A gene¹⁸, and it is now recognised that in a small number of children febrile seizures are the first sign that the child has an inherited seizure disorder¹⁹.

Associated factors

Population-based studies show a link between lower socioeconomic status and increased incidence of febrile seizures^{20,21}, possibly due to inadequate access to medical care and lack of information about febrile seizures. No significant link has been identified between febrile seizures and perinatal or maternal factors^{2,22,23}.

Precipitating factors

The height or duration of the fever may be important but there are problems in evaluating the temperature recordings because febrile seizures usually occur randomly at home. Viral infections are the most common cause of the fever that is associated with febrile seizures⁷. Synthesis of immunoglobulin in the CSF of children with febrile seizures has been demonstrated, suggesting that encephalitis may sometimes occur and not be recognised²⁴. There is evidence that human herpes virus-6 (HHV-6) is linked with exanthem subitum, a condition that is frequently complicated by febrile seizures²⁵, although HHV-6 infection can also occur independently of this²⁶. HHV-6B infection has been shown to be commonly associated with febrile status epilepticus, HHV-7 less frequently so. Together they accounted for one-third of the cases in a study of febrile status epilepticus, a condition associated with an increased risk of both hippocampal injury and subsequent temporal lobe epilepsy²⁷.

Bacterial infections may be associated with febrile seizures including urinary tract infections, shigella and pneumococcal bacteraemia. Children with bacterial meningitis sometimes have seizures and it is important to remember this when deciding whether or not to perform a lumbar puncture.

It has been shown that there are increased risks of febrile seizures on the day of receipt of DPT vaccine and 8-14 days after MMR vaccine, apparently not associated with long-term adverse consequences²⁸. A study in the UK found that 6-11 days after MMR vaccine there was an increased risk of complex febrile seizures lasting more than 30 minutes²⁹. However, a Danish study found that the increased risk of febrile seizures after MMR vaccination was small and transient. Also the long-term rate of epilepsy was not increased in children who had febrile seizures following MMR vaccination compared with children who had febrile seizures of a different aetiology³⁰.

Pathophysiology

The exact pathophysiology of febrile seizures is not fully understood and likely to be multifactorial. Children have a lower seizure threshold due to enhanced neuronal excitability of the immature brain³¹. This, in addition to fever, environmental triggers and genetic susceptibility involving a wide variety of genes including sodium channel expression, cortical and/or hippocampal excitability and hypothalamic dysregulation is likely to play a role³².

Outcome after febrile seizures

Deaths

Two large population-based studies found no deaths that were directly attributable to febrile seizures^{8,33}. The rate partly depends on how febrile seizures are defined - some studies have included seizures complicating known meningitis or encephalitis. A Danish population-based study showed that long-term mortality was not increased in children with febrile seizures, but there seemed to be a small excess mortality during the two years after complex febrile seizures. This finding was partly explained by pre-existing neurological abnormalities and subsequent epilepsy. They concluded that parents should be reassured that death after febrile seizures is very rare, even in high-risk children³⁴. A very small risk of death following complex febrile seizures, in particular febrile status epilepticus has been reported although this is not consistent within the literature³⁵.

Imaging studies.

MRI studies post prolonged and/or focal febrile seizures^{36,37}, and febrile status epilepticus³⁸, have reported large hippocampal volumes and normal T2 relaxation time suggesting hippocampal oedema.

Kuks *et al* studied 107 patients with drug resistant epilepsy using high-resolution volumetric MRI³⁹. Of these patients 45 had focal or diffuse hippocampal volume loss and there was a strong association between hippocampal sclerosis and a history of childhood febrile seizures. The authors pointed out that this association does not prove a causal relationship and that 64% of their patients with hippocampal volume loss gave no history of febrile seizures, so if childhood febrile seizures cause some cases of hippocampal sclerosis this cannot be the only mechanism.

Scott *et al*⁴⁰ performed diffusion-weighted magnetic resonance studies and found evidence of early vasogenic oedema after febrile seizures. They concluded that their findings were most consistent with a pre-existing hippocampal abnormality predisposing to febrile seizures. A Finnish MR study showed that the occurrence of mesial temporal sclerosis after prolonged febrile seizures was uncommon⁴¹. A prospective study in the United States found that after febrile status epilepticus (lasting 30 minutes or more) 11.5% of cases had definitely or equivocally abnormal increased T2 signal in MRI scans of the hippocampus compared with none in the control group. A substantial number also had abnormalities in hippocampal development. A follow-up study of this group found evidence that the hippocampal T2 hyperintensity represents acute injury often evolving to a radiological appearance of hippocampal sclerosis after one year⁴². Longer follow-up is needed to determine the relationship of these findings to temporal lobe epilepsy.

Post-mortem findings

Historical post-mortem studies from children who died after prolonged 'febrile seizures' describe neuronal necrosis, particularly affecting cerebral cortex, the hippocampi and the cerebellum^{43,44}. These authors, however, were describing extreme cases that were far from typical of the majority of febrile seizures. These studies also predate the well established prehospital treatments in developed countries for children with prolonged seizures and standardised guidelines for hospital treatment of prolonged seizures.

A retrospective study of patients with temporal lobe epilepsy reported on the pathological findings in the resected temporal lobes of 100 adults with refractory temporal lobe epilepsy⁴⁵. About half had 'mesial temporal sclerosis' which varied from loss of nerve cells in the Sommer (H1) sector of the hippocampus to wider involvement of the temporal lobe. In 40% of the patients with mesial temporal sclerosis there was a history of 'infantile seizures', suggesting a causal relationship.

Febrile recurrences

'Recurrence' in this context means more than one episode of febrile seizure, as opposed to 'multiple' which means more than one seizure during an episode of fever. Berg *et al* performed a meta-analysis and found that the overall risk of a recurrence was 34.3%⁴⁶. Young age at onset (one year or less) and a family history of febrile seizures predicted increased risk. Focal, prolonged and multiple seizures were only associated with a small increase. Other studies have found similar results. Most recurrences occur within three years of the first²⁴.

Subsequent afebrile seizures

The UK National General Practice Study of Epilepsy followed up children with febrile seizures for a mean of 21.6 years and found that 6% developed epilepsy over the whole follow-up period. The risk seemed to decrease with time⁴⁷. This risk of epilepsy is similar to that of a large US prospective cohort study that reported a 7% risk of afebrile seizures until the age of 25 years old⁴⁸. Risk can be stratified further depending on the type of febrile seizure. Those with simple febrile seizures had a 2.4% risk of afebrile seizures compared to those with complex febrile seizures whose risk relates to the number of complex features (6–8% risk if one complex feature, 17–22% risk if two complex features and 49% risk if three complex features).

Additional risk factors for the subsequent development of epilepsy include family history of epilepsy, short duration of fever prior to the seizure and pre-disposing neurodevelopmental abnormalities^{3,6,7,49–52}.

Type of afebrile seizure after febrile seizures

As discussed above, some studies suggest that febrile seizures can cause temporal lobe damage and lead to afebrile focal seizures. Annegers *et al* identified that children with febrile seizures had a higher risk of focal rather than generalised afebrile ('unprovoked') seizures⁴⁸. The prognostic factors for focal and generalised seizures were different. Febrile seizures that were focal, repeated or prolonged were strongly associated with focal afebrile seizures, whereas only the number of febrile seizures was significantly associated with generalised-onset seizures. Verity and Golding also reported an association between the occurrence of focal febrile seizures and later afebrile focal seizures¹⁰. In contrast to this, population-based studies have shown that the distribution of generalised and focal seizures in those that have had febrile seizures was similar to that in the general population, i.e. there was no excess of focal seizures in the febrile seizure group^{53,54}. This suggests that febrile seizures do not contribute appreciably to the occurrence of focal seizures.

Cognitive outcome

Population-based studies in the UK have found no difference in intellectual outcome between children (with no underlying neurological impairment) who had febrile seizures and their peers^{22,55}. Specific mild cognitive difficulties have however been described. Martinos *et al* reported that recognition memory is impaired in children after prolonged febrile seizures⁵⁶. Children were observed to have deficiencies in recognising a face after a five-minute delay approximately one-year post seizure; this was associated with relatively small hippocampal volumes in those children⁵⁰. Increased risk of speech delay has been reported in children following recurrent febrile seizures⁵⁷. Mildly increased rates of Tourettes⁵⁸, Attention Deficit Hyperactivity Disorder⁵⁹ and Autistic Spectrum Disorder⁶⁰ have been reported following febrile seizures, however these results are inconsistent and require further exploring.

With regards to behaviour outcome, in the UK based Child Health and Education Study (CHES) cohort a comprehensive assessment at ten years of age found that the behaviour of children with febrile seizures differed very little from their peers⁵⁶.

Outcome after febrile seizures – conclusions

Authors who report a poor outcome tend to have studied selected groups of children attending specialised hospitals or clinics. Some have included children who have had seizures complicating meningitis or encephalitis, or children that had developmental or neurological difficulties before they had their first febrile seizure. In contrast population-based studies that have looked at a less selected group of children give a much more positive view. Such studies show that most children with febrile seizures are neurotypical individuals who have simple febrile seizures, the majority of which do not recur. In such children there is little evidence of long-term effects on behaviour or intelligence and the increased risk of later epilepsy is slight. The minority of children have complex febrile seizures and for most of them the outlook is good. However, within this group there are a few children who are at particular risk of having later epilepsy, the risk being greatest for those who have febrile seizures with focal features, which tend to be prolonged and to occur in the younger children.

Clinical characteristics

Febrile seizures are tonic-clonic, clonic or possibly hypotonic in type. Most are brief and bilateral, but long-lasting and/or focal (unilateral) febrile seizures do occur: 70–75% of these are the initial febrile seizure experienced by the child⁵⁹.

Table 1. Characteristics of simple and complex febrile seizures⁴.

SIMPLE	COMPLEX
Generalised convulsive	Focal (one side of the body or one limb)
Less than 15 minutes	More than 15 minutes
No recurrence within 24 hours or within same febrile illness	Recurrence within 24 hours or within same febrile illness
Complete recovery within 1 hour	Incomplete recovery within 1 hour

Simple febrile seizures are the commonest type of febrile seizure. They are brief (<15 minutes) generalised seizures that do not occur more than once during a single febrile episode (see Table 1.). Some just consist of staring, perhaps accompanied by stiffening of the limbs and they may not cause the parents great concern. In the CHES birth cohort about 40% were not considered sufficiently severe to necessitate admission¹⁰. Approximately two-thirds of the children suffered only one febrile seizure.

Complex febrile seizures may be more severe than simple febrile seizures - in the CHES cohort¹⁰ 95 children (25% of the children with febrile seizures) had complex seizures and 78% of them were admitted to hospital - a higher proportion than was found in those with simple seizures. In these 95 children the complex features were as follows: 55 (58%) multiple, 32 (34%) prolonged and 17 (18%) focal (some had more than one complex feature). It is important to emphasise that the most severe attacks made up a very small proportion of all febrile seizures.

Management

Introduction

Groups of experts have published guidelines on the management of febrile seizure, the most recent of which was from NICE³. The American Academy of Pediatrics have published guidelines on both the neurodiagnostic evaluation of children with febrile seizures and long-term management^{2,59}. Many hospitals have local guidelines due to the frequency with which children present with febrile seizures.

Initial assessment

First the seizure should be stopped if it is continuing using standard prolonged seizure protocols.

The recommendations below are from the 2018 NICE guidelines³:

- Assess for red flag symptoms and signs suggesting a serious or life-threatening cause such as meningitis/meningococcal disease or encephalitis, and manage appropriately.

Ask about:

- If fever was associated with the seizure
- Reported parental perception of fever should be accepted as a valid indicator of fever
- Be aware that fever can occur any time during or after a seizure, and the majority of febrile seizures occur within 24 hours of fever onset
- When the fever started, peak temperature and duration, and any associated symptoms to suggest an underlying cause of febrile illness
- The relationship of the onset of fever to the seizure
- The characteristics and duration of the seizure, to help classify whether it is simple or complex
- The duration of any post-ictal drowsiness
- Any previous seizure episodes
- Any recent antibiotic use (may mask signs of central nervous system infection)
- Any recent immunizations, missed immunizations, or unknown immunization history
- Neurodevelopmental history and any concerns
- Whether the child attends daycare such as nursery (source of potential exposure to infection)
- Any family history of febrile seizures or epilepsy.

Examine the child:

- Assess the level of consciousness, and check for any focal neurological deficit such as weakness of the hand, arm, or leg
- Check the temperature after the seizure has ended
- A temperature of more than 38°C is generally considered significant
- Assess fluid status and for signs of dehydration
- Assess for other signs to identify the underlying cause of febrile illness and manage appropriately
- Assess for stigmata of a neurocutaneous or metabolic disorder suggesting an alternative cause for seizure
- Be aware that investigations are not usually needed in primary care
- Consider measuring blood glucose if a child cannot be roused or is having an acute seizure episode, if possible and appropriate
- Consider urine dipstick analysis and urine microscopy and culture if there is no clear focus for infection and the underlying cause of fever is uncertain.

When should I admit or refer a child following febrile seizure?

Arrange emergency ambulance transfer to Accident and Emergency if:

- There is suspected meningitis/meningococcal disease, or encephalitis
- There is another suspected serious or life-threatening cause of fever, such as pneumonia or sepsis.

Arrange immediate hospital assessment by a paediatrician if:

- It is the first presentation of febrile seizure (or a subsequent febrile seizure and the child has not had previous specialist assessment)
- The child is less than 18 months of age (clinical signs of central nervous system infection may be subtle or absent)
- There is diagnostic uncertainty about the cause of the seizure
- There are any features of a recurrent complex febrile seizure
- There is any focal neurological deficit
- There was a decreased level of consciousness prior to the seizure
- The child has recently taken antibiotics (may mask the signs of central nervous system infection)
- There is parental/carer anxiety and/or difficulty coping.

Consider urgent hospital assessment for a period of observation if:

- The child has unexplained fever and no apparent focus of infection
- Arrange referral to a paediatrician or paediatric neurologist for further assessment, the urgency depending on clinical judgement, if:
- The child has neurodevelopmental delay and/or signs of a neurocutaneous syndrome or metabolic disorder.

Investigations

'No investigations are routinely necessary in all children after a febrile seizure', according to the RCP/BPA Joint Working Group⁶⁰. Although somewhat dated this statement still seems to be the consensus view. It may be appropriate to check the blood glucose concentration or the electrolytes in some children with continuing seizures. Undertaking lumbar puncture is a clinical decision and will depend on any signs of meningitis, clinical description of the seizure, drowsy or irritable child, child who has already received antibiotics and age of child (more likely if <18 months)^{2,60}.

EEG

EEGs are not helpful in assessing the prognosis of children who have simple febrile seizures² but may be indicated in the child with prolonged or complex febrile seizures, afebrile recurrences or any neurological impairments/delay³.

Brain imaging

A child with a preceding or underlying neurological problem may first come to medical attention because of a febrile seizure. Underlying pathology may therefore be suspected on the basis of the history or examination and it may then be appropriate to perform a scan to investigate. This situation will exist in only a minority of children with febrile seizures and brain imaging is therefore not routinely indicated in a child with a simple febrile seizure.

Prophylactic treatment

A large Cochrane review of 30 studies and 4256 children addressed the question of prophylactic drug management in febrile seizures assessing the use of intermittent and/or continuous use of zinc, antipyretics and antiepileptic medication including ibuprofen, acetaminophen, diclofenac, phenobarbitone, benzodiazepines, phenytoin, valproate and pyridoxine⁶¹. Although this study reported reduced rates of recurrent febrile seizures following intermittent diazepam and continuous phenobarbitone, the high adverse effect rate of 30% precludes the use of these in an essentially benign process. They conclude that there is no clinical benefit of continuous or intermittent treatment with zinc, antiepileptic or antipyretic medications in children with febrile seizures.

For the child with recurrent prolonged febrile seizures it may be appropriate to train the parents/carers to administer buccal midazolam or rectal diazepam during a seizure.

Summary

General outcome

Febrile seizures are common. The majority are simple febrile seizures - brief generalised seizures that occur just once in the lifetime of neurotypical children. The evidence is that most children who have febrile seizures of any type (simple or complex) have no consequence in terms of neurological outcome.

Subsequent epilepsy

For most children with febrile seizures the risk of later epilepsy is little different from that of the general population. A minority of children who have febrile seizures are at increased risk of developing epilepsy - those that have neurological or developmental difficulties before the seizures and some of those who have febrile seizures with complex features, particularly if focal.

Initial management

Most febrile seizures stop spontaneously and not all children need to be admitted to hospital. It is reassuring if the child seems neurologically appropriate following the seizure. However, prolonged seizures should be stopped by appropriate acute treatment and if there is any other concern about the child's neurological state hospital assessment is appropriate. A lumbar puncture may be necessary to exclude meningitis in the minority of cases, particularly in children younger than 18 months. Ideally this decision should be made by an experienced doctor. Investigations are not routinely indicated after febrile seizures - the EEG is not helpful and brain scans are rarely indicated.

Subsequent medication

If febrile seizures are prolonged it may be appropriate to teach parents to administer buccal midazolam or rectal diazepam at home to prevent further prolonged episodes. There is no indication for the use of intermittent and/or continuous antipyretics or anticonvulsants in reducing the risk of further febrile seizures.

Information for carers

Many parents/carers are very distressed when they witness febrile seizures in their children and it should be a priority to inform them about the essentially benign nature of most febrile seizures. When assessing the prognosis it is relevant to consider the type of febrile seizure and the clinical context in which it occurs, but parents can be reassured that for the majority of children with febrile seizures the outcome is good and that medication is rarely indicated. Ideally, written information should supplement the interview and there are now excellent websites (e.g. <https://www.nhs.uk/conditions/febrile-seizures/>) and videos that provide advice and support for parents.

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CHAPTER 9

Benign childhood seizure susceptibility syndromes

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Introduction

Benign childhood focal seizures and related idiopathic epileptic syndromes affect 25% of children with non-febrile seizures and constitute a significant part of the everyday practice of paediatricians, neurologists and electroencephalographers. They comprise three identifiable electroclinical syndromes recognised by the International League against Epilepsy (ILAE)¹: rolandic epilepsy which is well known; Panayiotopoulos syndrome (PS), a common autonomic epilepsy, which is currently more readily diagnosed; and the idiopathic childhood occipital epilepsy of Gastaut (ICOE-G) including the idiopathic photosensitive occipital lobe epilepsy, a less common form with uncertain prognosis. There are also reports of children with benign focal seizures of predominantly affective symptoms, and claims have been made for other clinical phenotypes associated with specific interictal EEG foci, such as frontal, midline or parietal, with or without giant somatosensory evoked spikes (GSES). Neurological and mental states and brain imaging are normal, though because of their high prevalence any type of benign childhood focal seizures may incidentally occur in children with neurocognitive deficits or abnormal brain scans. The most useful diagnostic test is the EEG. In clinical practice, the combination of a normal child with infrequent seizures and an EEG showing disproportionately severe spike activity is highly suggestive of these benign childhood syndromes².

All these conditions may be linked together in a broad, age-related and age-limited, benign childhood seizure susceptibility syndrome (BCSSS) which may be genetically determined³. Details of original studies, numerous case histories and published reports not cited here can be found in our previous reviews^{2,4-7}.

Rolandic epilepsy (benign childhood epilepsy with centrotemporal spikes)

Rolandic epilepsy is the best known and commoner benign childhood focal epilepsy^{2,8-11}. The age of onset ranges from one to 14 years with 75% starting between 7-10 years. There is a 1:5 male predominance, prevalence is around 15% in children aged 1-15 years with non-febrile seizures and incidence is 10-20/100,000 children aged 0-15 years¹²⁻¹⁷.

Clinical manifestations

The cardinal features of rolandic epilepsy are focal seizures consisting of unilateral facial sensory-motor symptoms (30% of patients), oro-pharyngo-laryngeal symptoms (53%), speech arrest (40%) and hypersalivation (30%)^{2,8-11,18-20}. Ictal manifestations indicative of temporal lobe involvement does not occur in rolandic epilepsy and the term 'centrotemporal' refers only to the spike topography, partly a misnomer (see EEG section below). Hemifacial sensory-motor seizures are mainly localised in the lower lip and may spread to the ipsilateral hand. Motor manifestations are clonic contractions sometimes concurrent with ipsilateral tonic deviation of the mouth, and sensory symptoms consist of numbness in the corner of the mouth. Oro-pharyngo-laryngeal symptoms are unilateral sensory-

motor symptoms of numbness or paraesthesias (tingling, prickling or freezing) inside the mouth, associated with strange sounds, such as death rattle, gargling, grunting and guttural sounds.

Hypersalivation, a prominent autonomic manifestation, is often associated with hemifacial seizures, oro-pharyngo-laryngeal symptoms and speech arrest. The child is actually anarthric, unable to utter a single intelligible word and attempts to communicate with gestures.

Consciousness and recollection are fully retained in more than half (58%) of rolandic seizures. In the remainder, consciousness becomes impaired during the ictal progress and in one-third there is no recollection of ictal events. Progression to hemiconvulsions or generalised tonic-clonic seizures (GTCS) occurs in around half of children and hemiconvulsions may be followed by post-ictal Todd's hemiparesis². Consciousness and recollection are fully retained in more than half (58%) of rolandic seizures. In the remainder, consciousness becomes impaired during the ictal progress and in one-third there is no recollection of ictal events.

Three-quarters of rolandic seizures occur during non-REM (rapid eye movement) sleep, mainly at sleep onset or just before awakening.

Rolandic seizures are usually brief, lasting for 1–3 minutes. Focal motor, hemiconvulsive and generalised convulsive status epilepticus are rare at around 5%^{2,21,22}. Opercular status epilepticus usually occurs in children with atypical evolution^{23–25} or may be induced by carbamazepine or lamotrigine^{26,27}. This state lasts for hours to months and consists of ongoing unilateral or bilateral contractions of the mouth, tongue or eyelids, positive or negative subtle perioral or other myoclonus, dysarthria, speech arrest, difficulties in swallowing, buccofacial apraxia and hypersalivation.

Other seizure types

Despite prominent hypersalivation, focal seizures with primarily autonomic manifestations (autonomic seizures) are not considered part of the core clinical syndrome of rolandic epilepsy. However, some children may present with independent autonomic seizures or seizures with mixed rolandic-autonomic manifestations including emesis (see below, relations between rolandic epilepsy and PS).

Primarily GTCS are considered part of rolandic epilepsy by the ILAE1 and their occurrence cannot be excluded. However, from the published ictal recordings^{2,10,28} and the electroclinically unequivocal focal nature of rolandic epilepsy, it can be inferred that at least the majority of the GTCS follow rolandic activation and are therefore secondarily GTCS. Short-lived initial focal symptoms may pass unnoticed in daytime GTCS and are bound to be missed in nocturnal GTCS.

Electroencephalography

By definition, centrottemporal spikes (CTS) are the hallmark of benign childhood epilepsy with CTS. However, although called centrottemporal, these spikes are mainly localised in the C3 and C4 (high central) or C5 and C6 (low central) supra-sylvian and not temporal electrodes^{2,29}. CTS are often bilateral and typically activated by drowsiness and slow (non-REM) sleep, but not by overbreathing. Rarely, children with rolandic epilepsy may have normal EEG, CTS may be very small or they may appear only during non-REM sleep (3–35%)². In serial EEGs of the same child, CTS may occur right or left, infrequently or frequently, and appear small or giant, alone or with spikes in other locations. The incidence of extra-rolandic spikes in rolandic epilepsy is not precisely known but may be high when these are sought².

Dipole EEG^{30–32}, magnetoencephalography (MEG)^{33,34} and functional MRI³⁵ studies have demonstrated that the main negative spike component of CTS is usually modelled by a single and stable tangential dipole source with the negative pole maximum in the central region and the positive pole maximum in the frontal region.

Brief 1–3 second generalised bursts of 3–5 Hz slow waves with intermixed small spikes without associated overt clinical symptoms may occur in about 4% of patients with rolandic epilepsy^{2,36}. Typical 3 Hz spike-wave discharges and absence seizures are rare^{2,36,37}, though a high incidence of them has been reported³⁸.

CTS are diagnostic markers of benign rolandic epilepsy only in a suggestive clinical presentation. Their frequency, location and persistence do not determine the clinical manifestations, severity and frequency of seizures or the prognosis. It is well established that CTS are not specific to rolandic epilepsy^{2,39} as they:

- occur in 2–3% of normal school-aged children, of whom less than 10% develop rolandic seizures^{40–43}
- are common among relatives of children with rolandic epilepsy^{44,45}
- may occur in a variety of organic brain diseases with or without seizures, such as cerebral tumours, Rett syndrome, fragile X syndrome and focal cortical dysplasia^{2,39}
- may incidentally be found in non-epileptic children with various symptoms, such as headache, speech, and behavioural and learning difficulties⁴⁰.

Somatosensory stimulation is common form of activation of CTS (10–20%)^{2,46–49} and evokes GSES, which correspond to mid- or long-latency somatosensory evoked potentials⁵⁰. GSES, like spontaneous CTS, occur in children with or without seizures and disappear with age.

There have been around 20 reported ictal EEGs of rolandic seizures showing an initial paucity of spontaneous CTS before the onset of the ictal discharge, which appears contralateral to the clinical manifestations in the rolandic regions and consists of slow waves intermixed with spikes^{2,10,51}. GTCS, when they occurred, were preceded by focal clinical and EEG features^{2,10,28}.

Aetiology

Rolandic epilepsy is genetically determined although conventional genetic influences may be less important than other mechanisms^{52,53}. There is evidence of linkage with chromosome 15q14⁵⁴. Autosomal dominant inheritance with age-dependent penetrance refers to the EEG CTS and not to the clinical syndrome of rolandic epilepsy^{44,45}. Siblings or parents of patients with rolandic epilepsy may rarely have the same type of seizures or other phenotypes of BCSSS, such as PS. Reported occurrence of febrile seizures ranges from 10–20%⁵⁵.

Pathophysiology

As indicated by the distribution of centrottemporal spikes, the epileptogenic zone in rolandic epilepsy involves neuronal networks within the rolandic cortex surrounding the central fissure bilaterally. This is congruent with the seizure symptomatology (symptomotogenic zone) and in agreement with those described by Penfield and Rasmussen⁵⁶ during electrical stimulation of the lower part of the precentral and postcentral gyrus in man.

The speech arrest is due to anarthria attributed to loss of the power and co-ordination of the musculature responsible for the articulation of words. There is no impairment of the cortical language networks. Hypersalivation most probably relates to the involvement of the superior bank of the sylvian fissure⁵⁷, but defining ictal symptomotogenesis by plotting the simple topographic co-ordinates of an ictal discharge can hardly explain the high prevalence of hypersalivation in benign rolandic epilepsy compared to its exceptional only occurrence in adults with symptomatic foci of similar topography. Nor can it explain the opercular status epilepticus, with the speech arrest lasting several hours, drooling and bilateral regional twitching that is associated with diffuse

or bilateral rolandic spike-wave activity, but does not propagate in a conventional way and does not involve other systems like, for instance, the motor strip or the language function. Therefore, at variance with the symptomatic adult focal epilepsies of comparable but more discretely localised topography, rolandic epilepsy reflects an age-related maturational instability of the lower rolandic (somatosensory) cortex that represents the face and the oropharynx bilaterally⁷.

Evolution and prognosis

The prognosis for rolandic seizures is invariably excellent, with probably less than 2% risk of developing absence seizures and less often GTCS in adult life^{2,20,38,58-62}. Remission occurs within 2-4 years from onset and before the age of 16 years. The total number of seizures is low, the majority of patients having fewer than 10 seizures; 10-20% have just a single seizure. About 10-20% may have frequent seizures, but these also remit with age.

Children with rolandic seizures may develop usually mild and reversible linguistic, cognitive and behavioural abnormalities during the active phase of the disease⁶³⁻⁶⁸. These may be worse in children with onset of seizures before eight years of age, high rate of occurrence and multifocal EEG spikes⁶⁹⁻⁷¹. The effect of antiepileptic drugs (AEDs), the impact of stigmatising because of epilepsy, bias in selection of the most serious cases and other factors have not been excluded in most of these studies. The development, social adaptation and occupations of adults with a previous history of rolandic seizures was found normal^{58,59}.

Rarely (<1%) rolandic epilepsy may evolve to more severe syndromes with linguistic, behavioural and neuropsychological deficits, such as Landau-Kleffner syndrome, atypical focal epilepsy of childhood or epilepsy with continuous spike and wave during sleep (CSWS)²⁵, as explained later in this assessment.

Panayiotopoulos syndrome

Panayiotopoulos syndrome (PS) is a common, childhood-related, susceptibility to autonomic seizures confirmed in long-term studies of over 1000 children worldwide^{4,72-82}. PS is defined as 'benign age-related focal seizure disorder occurring in early and mid-childhood. It is characterised by seizures, often prolonged, with predominantly autonomic symptoms, and by an EEG that shows shifting and/or multiple foci, often with occipital predominance'⁸³. 'Early onset benign childhood occipital epilepsy', often used as synonymous with PS^{1,84}, does not represent the wide clinical, EEG and pathophysiological spectrum of PS which is far beyond the occipital neocortex⁸⁵.

Onset is from age 1-14 years with 76% starting between 3-6 years. Both sexes are equally affected. Prevalence of PS may be high, though this is practically absent in designed controlled epidemiological studies^{16,86-89} which is understandable as this syndrome was only recently formally recognised, its features imitate many other conditions, and it often manifests with a single seizure only. In the original cohort of Panayiotopoulos in 1988, prevalence was around 13% in children aged 3-6 years with one or more non-febrile seizures, and 6% in the age group 1-15 years. These figures may be higher if children who are currently considered to have atypical clinical presentation are included in the syndrome^{4,90}. A recent study found that PS is the most common specific cause of non-febrile status epilepticus in childhood⁹¹.

Clinical manifestations

The hallmark of PS is ictal autonomic aberrations that may involve any function of the autonomic system and mainly emesis (70-80% of seizures). The following description of clinical manifestations of PS is based on a synthetic analysis of available clinical historical data as perceived by patients and witnessed by observers from our records and those provided in the literature⁴. Therefore, they may not accurately represent their true prevalence and sequence in PS.

Ictal autonomic symptoms

Seizures commonly commence with autonomic manifestations (80-90%) while consciousness and speech, as a rule, are preserved. Ictus emeticus (nausea, retching, vomiting) culminates in vomiting in 74-82% of seizures; in others, only nausea or retching occurs, and, in a quarter, emesis may not be apparent. Emesis is usually the first apparent ictal symptom, but it may also occur long after the onset of other manifestations. Other autonomic manifestations include pallor (93%), incontinence of urine (19%) and faeces (3%), hypersalivation (10%), mydriasis (7%) and less often miosis (2%), coughing and abnormalities of intestinal motility (3%). Breathing (7%) and cardiac irregularities are rarely reported though they may be common in mild forms. Tachycardia is a common finding, sometimes at the onset of ictal EEG^{75,92-94}. Cardiorespiratory arrest is rare, probably occurring in 1 per 200 individuals (four possible cases out of around 1000 patients with PS have been reported)^{4,83,95}. Raised temperature has been documented in a few cases after seizure onset. Cephalic auras of discomfort and odd sensations or headache commonly occur with other autonomic symptoms at seizure onset.

Syncope-like manifestations occur in at least one-fifth of seizures^{4,83,90,96}. The child becomes 'completely unresponsive and flaccid like a rag doll' which may precede, be concurrent with other seizure symptoms, or be the sole manifestation of a seizure^{4,75}. They may occur while the patient is standing, sitting, lying down or asleep and last from 1-2 minutes to half an hour¹⁹⁵.

Ictal behavioural changes

Restlessness, agitation, terror or quietness, may appear at the onset of seizures, often in combination with other autonomic manifestations.

Ictal non-autonomic symptoms

Pure autonomic seizures and pure autonomic status epilepticus appear to occur in 10% of patients. They commence and terminate solely with autonomic symptoms. In all other seizures, autonomic manifestations are followed or occasionally start with conventional seizure symptoms. The child gradually or suddenly becomes confused and unresponsive. Unilateral deviation of the eyes is common (60-83%), occur with or without vomiting, seldom happens at onset and may be brief or lengthy. In some patients eyes open widely and remain in mid-position instead of deviating to one side.

Other ictal symptoms include speech arrest (8-13%), hemifacial convulsions (6-13%), visual hallucinations (6-10%), oro-pharyngo-laryngeal symptoms (3%), unilateral drooping of the mouth (3%) and rarely (1%) eyelid or limb jerks, nystagmus and automatisms. The seizures may end with hemic convulsions often with jacksonian marching (19-30%), or generalised convulsions (21-36%).

Duration of seizures and precipitating factors

The seizures are usually lengthy of over six minutes and almost half of them last for more than 30 minutes to many hours, thus constituting autonomic status epilepticus^{4,96}. Lengthy seizures are equally common in sleep and wakefulness. Even after the most severe seizures and status, the patient is normal after a few hours' sleep. There is no record of residual neurological abnormalities. Hemic convulsive or convulsive status epilepticus is rare (4%).

Two-thirds of seizures start in sleep. Many seizures have been witnessed while travelling in a car, boat or aeroplane. The reason for this may be because in these circumstances the child easily falls asleep, seizures are more likely to be witnessed and because travelling also precipitates motion sickness, to which children are particularly susceptible.

Intra-individual seizure variability

The same child may have brief and lengthy seizures, diurnal and nocturnal, with marked, inconspicuous, or even without any autonomic changes^{4,74-80,82}. Even cardinal symptoms (such as

vomiting or eye deviation) may be present in one but absent in another seizure. Seizures without autonomic manifestations are rare (7%) and occur in patients who also have additional autonomic seizures⁴. Ictal video EEG recordings have documented that autonomic symptoms and signs may vary between seizures of the same child⁹³. There is no correlation between ictal semiology and topography of inter-ictal spikes.

Aetiology

PS, like rolandic epilepsy, is probably genetically determined. Usually, there is no family history of similar seizures, although siblings with PS or PS and rolandic epilepsy have been reported^{74,77,79,80,97}. There is a high prevalence of febrile seizures (about 17%)⁴.

SCN1A mutations have been recently reported in a child⁹⁸ and two siblings⁹⁷ with relatively early onset of seizures, prolonged time over which many seizures have occurred and strong association with febrile precipitants even after the age of five years. This is an area that needs further attention but may indicate that SCN1A mutations contribute to a more severe phenotype of PS.

Pathophysiology

Autonomic symptoms of any type are often encountered in seizures, whether focal or generalised, in adults or children^{96,99,100}. They are generated by activation or inhibition of parts of the central autonomic network that involves the insular cortex, medial prefrontal cortex, amygdala, hypothalamus, and ventrolateral medulla¹⁰⁰. The resultant autonomic disturbances depend on the brain areas involved in seizure onset or propagation, and appear as single or multiple symptoms, some of which may be of localising value¹⁰¹.

In PS, the neuroanatomical and neurophysiological underpinnings of autonomic manifestations are unknown. Any explanation of the pathophysiology of PS should take into account two pieces of evidence that converge from clinical, EEG and magneto-encephalographic studies: first, the epileptogenic zone in PS is wide and bilateral with multifocal pockets in cortical areas surrounding major fissures such as calcarine, central or sylvian¹⁰²⁻¹⁰⁵; second, ictal autonomic symptomatology appears to pertain to any epileptogenic cortical onset zone, be this occipital, frontotemporal or frontal^{75,92-94,106}.

Autonomic seizures and autonomic status epilepticus with the symptomatology and sequence detailed in PS, appear to be specific for childhood^{96,107}. For example, in adults ictal vomiting occurs scarcely, and as a rule when consciousness is impaired following other focal mainly temporal lobe symptoms and is attributed to non-dominant mesial temporal lobe involvement¹⁰⁸⁻¹¹¹. In contrast, ictal vomiting in children is common, usually occurs when consciousness is intact without preceding focal cortical symptoms, and probably has no localising or lateralising value (see Electroencephalography, opposite). A possible explanation for these discrepancies may relate to the fact that children are constitutionally more vulnerable to emetic disturbances as exemplified by the 'cyclic vomiting syndrome', a non-seizure disorder of unknown aetiology that is also specific to childhood¹¹² and associated with autonomic dysfunction¹¹³. Thus, the preferential involvement of emetic and other autonomic manifestations in PS may be attributed to a maturation-related susceptibility of the central autonomic network^{4,107}. This is compounded by a multifocal cortical epileptogenic hyperexcitability that is also maturation related and may predominate in one brain area, which is often posterior. It is likely that central autonomic networks have a lower threshold to epileptogenic activation than those producing focal cortical semiology (occipital, frontal, central, parietal and less often temporal). Irrespective of the localisation of their onset, ictal discharges may activate the lower-threshold autonomic centres (and therefore produce autonomic manifestations) before other cortical regions of relatively higher threshold that generate focal cortical symptoms (sensory, motor, visual or other). Seizures remain purely autonomic if ictal neuronal activation of non-autonomic cortical areas fails to reach threshold; otherwise they consist of autonomic

and localisation-related cortical symptoms and signs that may only rarely occur from onset. This hypothesis may explain why similar autonomic manifestations may appear from anterior or posterior, right or left-brain onsets. As seizures primarily involve a particular system (the autonomic), PS may be considered as an electroclinical example of 'system epilepsy'⁷.

Syncopal-like attacks may be difficult to explain in individual cases. They may be a distinct seizure type similar to atonic seizures but on some occasions, they may be due to cardiac asystole (ictal syncope) generated by the seizure discharge¹⁹⁵.

Electroencephalography

Inter-ictal EEG findings show great variability^{4,6,73,75,77-80,82,83}. In about 90% of cases, the EEG reveals mainly multifocal, high amplitude, sharp slow wave complexes that may appear in any area, often shifting from one region to another in the same or the contralateral hemisphere in sequential EEGs of the same child. Occipital spikes predominate but they do not occur in one-third of patients. Occipital paroxysms in their classical form with fixation off sensitivity (FOS) are even rarer. Clone-like, repetitive, multifocal spike-wave complexes may be characteristic features when they occur (19%)⁴. Brief generalised discharges of slow waves, intermixed with small spikes, may occur either alone (4%) or more often with focal spikes (15%). A single routine EEG may be normal in 10% of patients, and a few children have consistently normal wake EEGs before a diagnostic sleep recording. Sleep typically accentuates the spike abnormalities, and photosensitivity is practically absent.

As in benign rolandic epilepsy, the frequency, location and persistence of spikes do not determine the clinical manifestations, the duration, the severity and frequency of seizures or their prognosis. For instance, spikes may persist for many years after clinical remission or appear only once despite multiple EEGs. The multifocal potential for epileptogenesis in PS has also been documented by EEG dipole analysis¹⁰⁴ and magnetoencephalography, which have implicated areas along the parieto-occipital, calcarine and central sulci or in the frontal lobes^{102,103,105}.

In the few reported ictal EEGs, the discharges consist mainly of unilateral rhythmic slow activity, usually intermixed with fast rhythms and small spikes. They start in wider more often in posterior than anterior regions, quickly become diffuse and last for many minutes^{75,92-94,106}. The first ictal clinical symptoms become apparent long after the onset of the electrical discharge and present as tachycardia, breathing irregularities, coughing or emesis, which would be impossible to consider as seizure events without an EEG.

Differential diagnosis

PS is easy to diagnose because of the characteristic clustering of clinical seizure semiology, which is often supported by inter-ictal EEG findings. The main problem is to recognise emetic and other autonomic manifestations as seizure events, and not to dismiss them or erroneously consider them as unrelated to the ictus and as a feature of encephalitis, migraine, syncope or gastroenteritis, which is the reason for the belated recognition of this common syndrome^{4,73,114,115}. A most difficult situation that demands experienced evaluation is when a child is seen at the acute stage of a seizure when symptoms may dramatically accumulate in succession and the diagnosis of true encephalitis is possible. A history of a previous similar seizure or full recovery after a few hours of sleep is reassuring and may help to avoid unnecessary investigations and promote withdrawal of any medication that may have been initiated^{6,116}.

Approximately 10–20% of autonomic seizures and autonomic status epilepticus in children is due to heterogeneous cerebral pathology^{4,73}. These symptomatic cases are betrayed by abnormal neurological or mental state, abnormal brain imaging and background EEG abnormalities. PS is significantly different from rolandic epilepsy and ICOE-G, despite some overlapping clinical and/or EEG features and these are detailed in the relevant section of this paper.

Prognosis

PS is remarkably benign in terms of its evolution^{4,73-80} but autonomic seizures are of concern in the rare context of cardiorespiratory arrest^{4,83,5,96}. The majority of patients have a single or less than five seizures until remission. Only one-quarter have multiple and sometimes very frequent and prolonged seizures that may be resistant to treatment. Remission often occurs within 1-2 years of onset but probably 10% may have more protracted active seizure periods. One-fifth of patients develop rolandic and less often occipital or other seizures but these are also age related and remit⁴. Atypical evolution of PS similar to those described in rolandic epilepsy is rare probably less than 3%^{80,117-119}.

The risk of epilepsy in adult life appears to be no higher than in the general population^{4,80,83}.

Subtle neuropsychological deficits in some children during the active phase¹²⁰ may be syndrome-related symptoms in PS, but may also reflect effects of AEDs (most of the children were on AEDs including phenobarbital and vigabatrin) and/or other contributing factors. Prognosis of cognitive function is good even for patients with atypical evolutions⁸⁰.

Idiopathic childhood occipital epilepsy of Gastaut

ICOE-G is a relatively rare form of pure occipital epilepsy accounting for about 2-7% of benign childhood focal seizures^{2,74,76,121-130}. Age at onset ranges from 3-15 years, but most frequently it starts between 8-11 years. Both sexes are equally affected.

Clinical manifestations

Seizures are occipital and primarily manifest with elementary visual hallucinations, blindness or both^{2,121-124,126,127}. They are usually frequent, brief and diurnal.

Visual ictal symptoms

Elementary visual hallucinations are the commonest and most characteristic ictal symptom of ICOE-G. They are frequently the first and often the only seizure symptom. They develop rapidly within seconds and consist mainly of small multicoloured circular patterns that often appear in the periphery of a visual field, becoming larger and multiplying during the course of the seizure, frequently moving towards the other side. Ictal blindness is probably the second most common symptom after visual hallucinations. It is sudden, usually total and it is frequently the first and often the only seizure symptom in patients who may also have other visual seizures without blindness. Impairment of visual awareness is consistently reported by some patients before the appearance of visual hallucinations. Complex visual hallucinations such as faces and figures and visual illusions such as micropsia, palinopsia and metamorphopsia occur in less than 10% of patients and mainly after the appearance of other visual symptoms¹²².

Non-visual ictal occipital lobe symptoms

Non-visual occipital symptoms usually appear after the elementary visual hallucinations and these, in order of prevalence, are deviation of the eyes, eyelid fluttering or repetitive eye closures and sensory hallucinations of ocular movements^{2,121,122,124,126,127}.

Deviation of the eyes, often associated with ipsilateral turning of the head, is the most common (in about 70% of cases) non-visual ictal symptom. It usually starts after the commencement of visual hallucinations and may be mild, but more often it is forceful tonic and may progress to hemiconvulsions and GTCS. Some children may have seizures of eye deviation from the start without visual hallucinations and it is likely that these cases have a better prognosis^{74,130}. Other ocular manifestations may include unidirectional ocular clonic seizures (oculoclonic seizures) that are rare, and eyelid fluttering or repetitive eye closures that occur in about 10% of patients, usually at a later stage when consciousness is impaired. They signal an impending secondary GTCS.

Ictal headache, or mainly orbital pain, is a common ictal symptom, and in a small number of patients it may start before the first visual or other ictal occipital symptoms.

Consciousness is intact during the visual symptoms (simple focal seizures) but may be disturbed or lost in the course of the seizure, usually before or at the time of eye deviation or convulsions. Syncopal-like attacks are rare⁴.

Extra-occipital seizure progression

Elementary visual hallucinations or other ictal symptoms may progress to complex focal seizures (14%), hemiconvulsions (43%) or GTCS (13%)¹²². Complex focal seizures of temporal lobe symptomatology are extremely rare and may indicate a symptomatic cause¹²⁴. Ictal vomiting may occur with progression to the non-dominant temporal lobe¹³¹.

Post-ictal headache

Post-ictal headache, mainly diffuse, but also severe, unilateral, pulsating and indistinguishable from migraine headache, occurs in half the patients, in 10% of whom it may be associated with nausea and vomiting^{2,22,124,126}. This occurs immediately, or 5-10 minutes after the end of the visual hallucinations. The duration and severity of the headache appears to be proportional to the duration and severity of the preceding seizure, although it may also occur after brief simple visual seizures.

Seizure stereotype

For any one patient, in every seizure the elementary visual hallucinations have a fingerprint with a stereotypic appearance regarding morphology, colours, location, movement and other characteristics. Most patients also know at what stage of their ictal manifestations a secondarily GTCS may occur.

Duration and circadian distribution

Visual seizures are usually brief, lasting from a few seconds to 1-3 minutes if they occur alone without other occipital or extra-occipital spreading^{2,121,122,124-127}. However, a few patients with brief visual seizures may later develop lengthy visual seizures lasting for 10-20 minutes. Visual seizures are predominantly diurnal and occur at any time of the day, but some patients may also have infrequent seizures in sleep or on awakening.

Frequency of seizures

If untreated, the majority of patients experience frequent brief visual seizures ranging from several every day to one per week or month. However, propagation to other seizure manifestations, such as focal or generalised convulsions, is much less frequent occurring once per month, year or even rarer.

Precipitating factors and idiopathic photosensitive occipital epilepsy

This is a matter of inclusion criteria. Gastaut considers photosensitivity as part of ICOE-G^{121,122}, while the ILAE Task Force recognises 'idiopathic photosensitive occipital lobe epilepsy' as a syndrome of reflex epilepsy with age-related onset¹³². Reflex occipital seizures induced by television, video games, and intermittent photic stimulation (IPS) manifest with similar semiology as the spontaneous visual seizures^{5,131,133-136}. Deviation of the eyes, epigastric discomfort and vomiting, headache, and generalised convulsions may follow. Prognosis is uncertain. Some children may have only one or two seizures, but others may not remit. Inter-ictal EEG shows spontaneous and photically induced occipital spikes. Centrottemporal spikes may coexist. Ictal EEG documented the occipital origin and the spreading of the discharges to the temporal regions^{131,135}. There remain no other significant precipitating factors in ICOE-G if photosensitive patients are excluded. Despite FOS in EEG, only a few patients report seizure precipitation by going from bright light to darkness or by darkness itself¹³⁷.

Aetiology

There is an increased family history of epilepsies (21–37%) or migraine (9–16%)^{122,126,138} but familial ICOE-G appears to be rare^{139,140}.

Pathophysiology

The seizures are purely of occipital lobe origin. The epileptogenic zone involves wide and bilateral networks within the occipital lobes and this localisation is congruent with the symptomatogenic zone. Elementary visual hallucinations originate from the visual cortex, complex visual hallucinations from the junction of the occipital with the parietal and temporal lobes, formed visual illusions from the lateral occipital-posterior temporal junction and tonic deviation of the eyes from the medial occipital cortex, above or below the calcarine sulcus. Ictal blindness may reflect bi-occipital seizure spreading but this may not explain its sudden onset, without any other preceding manifestations. From the EEG standpoint, the occipital paroxysms are usually bilateral and synchronous because they are activated in both occipital regions by the elimination of fixation (FOS) and central vision⁷² and not by thalamocortical activation proposed by Gastaut and Zifkin¹²².

The mechanisms for post-ictal headache are unknown. It is likely that the occipital seizure discharge triggers a genuine migraine headache through trigeminovascular or brain-stem mechanisms^{124,141}.

Diagnostic procedures

By definition, all tests other than the EEG are normal. However, high-resolution MRI is mandatory, because symptomatic occipital epilepsy present with the same clinical-EEG manifestations.

Electroencephalography

The inter-ictal EEG shows occipital paroxysms^{121,122}, often demonstrating FOS^{72,142}. Because terminology is often unclear and FOS is not always tested, the prevalence of classical occipital paroxysms with FOS is uncertain and ranges between 100%¹²², 88%¹²⁶ and 19%². Some patients may have only random occipital spikes, whereas others may have occipital spikes only in sleep EEG and some may have a consistently normal EEG¹²⁴. Centrottemporal, frontal and GSES occur together with occipital spikes in around 20% of patients^{122,143}. IPS consistently elicits occipital spikes and/or generalised discharges in photosensitive patients.

As happens with the rolandic spikes, occipital spikes are not pathognomonic of any particular syndrome, because they also occur in a variety of organic brain diseases with or without seizures, in children with congenital or early onset visual and ocular deficits, and even in 0.5–1.2 % of normal pre-school age children^{39,40,144}. They are common in young children with a peak age at first discovery of 4–5 years, and ‘tend to disappear in adult life, and the subsidence of the EEG abnormality is usually accompanied by a cessation of seizures’^{40,144}.

There are many reported ictal EEGs^{92,121,122,133,145–148}. Seizure onset is preceded by regression of occipital paroxysms and is characterised by the sudden appearance of an occipital discharge that consists of fast rhythms, fast spikes or both and is of much lower amplitude than the occipital paroxysms. Elementary visual hallucinations relate to the initially fast spike activity and complex visual hallucinations may occur when the ictal discharge is slower. In oculoclonic seizures, spikes and spike-wave complexes are slower, and a localised ictal fast spike rhythm may occur before deviation of the eyes. Ictal EEG during blindness is characterised by pseudo-periodic slow waves and spikes, which differ from those seen in ictal visual hallucinations. There are usually no post-ictal abnormalities.

Differential diagnosis

The differential diagnosis of ICOE-G is mainly from symptomatic occipital epilepsy, migraine with aura, acephalgic and basilar migraine where misdiagnosis is very high^{2,124}.

Patients with symptomatic occipital epilepsy may often have symptoms identical to those of ICOE-G with normal neuro-ophthalmological examination and routine brain imaging. Thus, high-resolution MRI is required to detect subtle lesions¹⁴⁹. Occipital seizures of mitochondrial disorders, Lafora disease and coeliac disease should be considered^{2,84}.

The differential diagnosis of ICOE-G from migraine is usually easy if all clinical elements are properly assessed and synthesised. Contrary to visual seizures, visual aura of migraine develops slowly within minutes, lasts for 10–20 minutes and consists of mainly achromatic and linear patterns^{150–152}. Illustration of the visual symptoms of the attacks by the patient is a powerful tool in differential diagnosis and to inform objective analysis. Orbital pain in the ictal phase of visual hallucinations is typical of occipital seizures and does not occur in migraine. However, post-attack headache is common and similar for both occipital epilepsy and migraine. Basilar migraine attacks also develop slowly within minutes, last for 30–60 minutes and consist of mainly bilateral impairment of vision associated with, or followed by, neurological symptoms such as vertigo, tinnitus, ataxia, bilateral weakness and dysaesthesiae which do not occur in occipital lobe epilepsy¹⁴¹. Mistaking visual seizures for migraine attacks may be common in publications referring to controversial diagnostic terms such as ‘migralepsy’ and ‘basilar migraine with occipital paroxysms’. A critical review of such reported cases indicates that these are likely to be genuine occipital seizures imitating migraine¹⁴¹.

ICOE-G is distinctive from PS (Table 1) and the differences have been statistically validated² despite some overlapping features. A key point in the differential diagnosis is that seizure onset is primarily with visual symptoms in ICOE-G and with autonomic manifestations in PS.

Prognosis

The prognosis of ICOE-G is unclear, although available data indicate that remission occurs in 50–60% of patients within 2–4 years of onset^{122,124,126}. Seizures show a dramatically good response to carbamazepine in more than 90% of patients. However, 40–50% of patients may continue having visual seizures and infrequent secondarily GTCS. Rarely, atypical evolutions to epilepsy with CSWS and cognitive deterioration have been reported¹⁵³. Also rarely, children with ICOE-G may manifest with typical absence seizures, which usually appear after the onset of occipital seizures¹⁵⁴.

The performance scores for attention, memory and intellectual functioning were lower in patients with ICOE-G than control subjects though basic neurophysiological functions did not differ significantly¹⁵⁵.

Other phenotypes of BCSSS

There are reports of children suffering from benign childhood focal seizures with clinical-EEG manifestations that cannot be classified as rolandic epilepsy, PS or ICOE-G. They may represent rare, atypical or overlapping presentations of BCSSS.

Benign childhood seizures with affective symptoms

Benign childhood epilepsy with affective symptoms, reported in less than 40 patients, is a clinical phenotype of BCSSS with features common in both PS (behavioural and autonomic symptoms) and rolandic epilepsy (speech arrest and hypersalivation)^{156,157}. Onset is between 2–9 years of age and both sexes are equally affected.

Seizures manifest with terror and screaming, autonomic disturbances (pallor, sweating, abdominal pain, hypersalivation), chewing and other automatisms, speech arrest and mild impairment of consciousness. These are usually brief for 1–2 minutes, frequently occurring several times a day in wakefulness or sleep. One-fifth of patients have febrile seizures, and some may also have infrequent rolandic seizures. Generalised seizures do not occur.

The inter-ictal EEG shows high-amplitude frontotemporal and parietotemporal spikes that are exaggerated by sleep. Ictal EEG discharges are mainly localised in the frontotemporal, centrotemporal or parietal regions and are stereotypical for each patient.

The response to treatment is excellent and remission occurs within 1–2 years from onset. Behavioural problems may be prominent during the active stage of the disease but subside later with seizure remittance.

Benign childhood epilepsy with parietal spikes and frequent extreme somatosensory-evoked spikes
Benign childhood epilepsy with parietal spikes and frequent GSES^{46,47,158} has been proposed as another phenotype of BCSSS. The defining features are EEG spikes in the parietal regions, which are often elicited by tactile stimulation. However, GSES are not specific for any syndrome because they also occur in 10–20% of children with rolandic seizures⁴⁷, in a few patients with PS^{2,4} and in children with no seizures¹⁵⁹.

Versive seizures of the head and body, often without impairment of consciousness, are mainly diurnal and infrequent. Frequent seizures and focal status epilepticus are exceptional.

Remission usually occurs within one year from seizure onset, but EEG abnormalities may persist for longer.

Benign childhood focal seizures associated with frontal or midline spikes
Benign childhood focal seizures associated with frontal^{2,160,161} or midline spikes^{2,162} have been described and long follow-up reports have confirmed a benign course, although no systematic studies have been published. However, EEG spike foci specificity is questionable, as EEG spike foci of various locations (including frontal and midline) are also seen in rolandic epilepsy and more commonly in PS, and midline spikes are more common in children than in adults^{163,164}.

Recently ‘benign infantile focal epilepsy with midline spikes during sleep’ has been described as a new syndrome of BCSSS^{165,166}. Age at onset is in the first three years of life and both sexes are equally affected. Seizures consist mainly of staring, motion arrest, cyanosis, loss of consciousness and stiffening of the arms. Clonic convulsions and automatisms are rare. Seizures are brief from 1–5 minutes, mainly diurnal and are generally infrequent from 1–3 per year. There is a strong family history of undefined types of epileptic seizures with benign epilepsies prevailing.

Inter-ictal EEG abnormalities are seen only in non-REM sleep and consist of small, mostly singular, midline spikes. The prognosis is excellent, with remission of seizures, normal development and normalisation of the EEG before the age of four years.

Differential diagnosis between seizures and syndromes of BCSSS

The differential diagnosis between the main phenotypes of BCSSS is easy in their typical presentations (Table 1). Problems may arise in children with clinical symptoms that fall into two (or more) phenotypes or from overemphasising on EEG localisation. As in any other medical condition, a single symptom is of limited syndromic significance. The differential diagnosis requires that symptoms are meaningfully synthesised in regard to quality and quantity, chronological sequence, consistency, relation to other seizure manifestations, the circumstances of their appearance and the overall clustering of clinical-EEG manifestations.

Rolandic epilepsy vs Panayiotopoulos syndrome
Their differential diagnosis is usually easy (Table 1). However, there are some cases with overlapping features:

- (a) One-tenth of children with PS often have typical and lengthy autonomic seizures with concurrent rolandic features such as speech arrest, hemi-facial convulsions, hypersalivation and OPS but these appear after the onset of autonomic symptoms and emesis^{4,74–77,80}. Conversely, these ictal symptoms occur at onset and usually without autonomic symptoms in rolandic epilepsy.
- (b) One-tenth of children with PS develop pure rolandic seizures, either in parallel with autonomic seizures, or at a later age prior to final remission^{4,75,77,80}.
- (c) The topography of inter-ictal spikes may overlap. Covanis *et al*⁷⁹ studied 24 otherwise normal children with focal non-febrile seizures who had emetic manifestations in at least one seizure and CTS in at least one EEG; 21 (83%) had ictal semiology typical of PS but five also had concurrent rolandic symptoms and four later developed pure rolandic seizures. The other four children (17%) had typical rolandic seizures with concurrent ictus emeticus. Ohtsu *et al*⁸² found that in early-onset rolandic epilepsy vomiting usually happened in the middle of the ictus, seizures, neurocognitive and behavioural abnormalities were more frequent while focal status epilepticus and prolonged seizures were less common than in PS.
- (d) Of siblings one may have rolandic seizures and another PS and there is a high prevalence of febrile seizures in both^{4,74,75,0}.

Idiopathic childhood occipital epilepsy of Gastaut vs PS
The differentiation here is more straightforward (Table 1). The seizures of ICOE-G are purely occipital and as such start and often end only with occipital lobe symptomatology. Further, seizures are mainly brief, frequent and diurnal. Rarely, seizures may be longer and also occur in sleep but these are also fundamentally different to the rolandic epilepsy or the autonomic seizures and autonomic status epilepticus of PS.

Exceptionally ictal vomiting may occur in ICOE-G but this follows the appearance of visual symptomatology as it happens with reflex photosensitive occipital seizures^{131,135} and the same patient usually has frequent brief occipital seizures. Conversely, visual symptoms in PS, when present, are not prominent or stereotypic and by rule occur concurrently with other salient clinical manifestations after the seizure has started^{4,74,80,167,168}. From the EEG standpoint, occipital paroxysms or occipital spikes which characterise ICOE-G are also common in PS but these often occur with extra-occipital spikes and with shifting locations in sequential EEG. Further, ictal EEG is markedly different in these syndromes.

Reported difficulties in the differential diagnosis of ICOE-G and PS¹⁶⁹ may arise when assessing them on individual symptoms and features without considering quality, chronological sequence from onset, stereotypical appearance or not that may be common even amongst different disorders including migraine with aura (visual hallucinations, lengthy durations, vomiting and headache).

Further, the commonly quoted argument that PS is not essentially different from ICOE-G considering that ‘the younger the children are, the less likely they are to describe visual symptoms’¹³⁸ is not tenable: a) more than two-thirds of children with PS are older than four years and therefore able to describe their visual experiences; b) there is no difference in seizure presentation between younger and older children with PS.

A few patients with either PS or rolandic epilepsy may later develop purely occipital seizures as of ICOE-G^{4,70,171}. These cases are easy to diagnose and indicate the intimate links of these disorders within the framework of BCSSS.

BCSSS: a unified concept of benign childhood focal seizures

Rolandic epilepsy, PS, ICOE-G and other possible clinical phenotypes of benign childhood focal seizures are likely to be linked together by a genetically determined, functional derangement of the systemic brain maturation that is mild and age related (BCSSS)^{3,4}. They have distinctive characteristics, but they also share common clinical and EEG features: seizures are infrequent, usually nocturnal and remit within a few years from onset. Brief or prolonged seizures, even focal status epilepticus, may occur only once in the patient's lifetime. Despite the distinctiveness of their core clinical and EEG features, the natural histories of these syndromes may show significant reciprocity: some children with rolandic epilepsy may present autonomic seizures referable to PS (and vice versa) before remittance, while other may have alternate autonomic and rolandic seizures. Some seizures may be of mixed character, and certainly ictal autonomic manifestations, such as hypersalivation, emesis, headache and syncopal-like attacks that are unusual in other epileptic syndromes in children or adults, are frequent in BCSSS, and may predominate. Affected siblings may have the same or another type of benign childhood focal seizures and febrile seizures are common. EEG spikes are regional (bilateral and multifocal) than focal – and as a rule disproportionately abundant to the frequency of seizures – and there is a significant overlap of inter-ictal topographies.

There is no reason to suggest that these syndromes differ merely because an 'epileptogenic' focus is slightly anterior or posterior, lateral or medial to the central regions. The relevant ictal semiologies and EEG findings suggest that each one of these forms reflects constitutional hyperexcitability of a particular functional brain area or system: the lower rolandic (somatosensory) cortex that represents the face and the oropharynx bilaterally in benign rolandic epilepsy, the occipital areas (cortical visual system) in ICOE-G and of the central autonomic network bilaterally and diffusely in PS⁷. Therefore, all these conditions are linked together by a genetically determined, functional derangement of the systemic brain maturation that is mild and age related^{2,3}. This derangement is often clinically silent and presents in more than 90% of the susceptible children only with – also age-related – EEG sharp and slow waves; the remaining tenth of these children have infrequent focal seizures. A small number of susceptible children, with or without seizures, may also have minor and fully reversible neuropsychological symptoms that are rarely clinically overt and can be detected only by formal neuropsychological testing. Finally, in a very small number of patients (probably <1%) this disturbance of brain maturation may further evolve into a more aggressive clinical state with seizures, neuropsychological manifestations and EEG abnormalities of various combinations and severity, such as atypical benign focal epilepsy of childhood, Landau-Kleffner syndrome and epilepsy with CSWS.

This concept of BCSSS is in agreement with previously expressed views of 'functional epilepsies of maturation'¹⁷², 'multifactorial pathogenesis of epilepsies with benign focal epileptiform sharp waves'^{173,174}, 'selective rates of maturation of the different cortical areas'⁵⁷ and more recently of possible 'neurobiological relationships' between BCSSS and IGE⁸⁴.

BCSSS, febrile and other idiopathic focal seizures in neonates and infants

One of the most interesting aspects of benign childhood seizures is their striking age-related sequence that appears to reflect enhanced epileptogenicity of the developing brain, as a whole and also of its functional systems, in different stages of maturation. Benign neonatal and infantile seizures, rolandic epilepsy, PS, ICOE-G and other clinical phenotypes of BCSSS are specific to early life and do not occur in adults. This is also the case with most febrile seizures whose different genetic influences may explain their high prevalence amongst patients with BCSSS and other more severe types of epilepsy, including the febrile plus phenotypes and genotypes^{175,176}. It appears that there are three main periods of age-related childhood susceptibility to benign seizures: febrile, mainly generalised, convulsions first appear in early childhood at a peak age of around 18–22 months;

rolandic epilepsy and ICOE-G manifest with purely focal seizures and occur in late childhood age; PS presents with mainly autonomic seizures and covers the intermediate early childhood period with peak at four or five years. The neonatal and early infantile periods are not immune to focal seizure susceptibility either, as indicated by the benign neonatal seizures of the first few days of life¹⁷⁷, and the benign infantile focal seizures of Watanabe and Vigeveno¹⁷⁸. This point is exemplified by reports of children with neonatal seizures who later developed rolandic epilepsy¹⁷⁹ or PS^{5,77}.

BCSSS, Landau-Kleffner syndrome, epilepsy with CSWS and atypical benign partial epilepsy of childhood

Landau-Kleffner syndrome and epilepsy with CSWS¹⁸⁰ are now considered by the ILAE as an entity named 'epileptic encephalopathy of CSWS including Landau-Kleffner syndrome' with a common pathophysiological mechanism¹. Atypical benign partial epilepsy of childhood^{181,82} may be a mild form of epilepsy with CSWS¹⁸³. Epileptic encephalopathy of CSWS including Landau-Kleffner syndrome are functional disorders occurring at an age where cortical synaptogenesis with abundant axonal sprouting and elemental functional network is being established in the brain. Aggressive epileptogenic activity at this active period of brain organisation is detrimental for the establishment of appropriate neuronal connections, normal brain development and functioning¹⁸⁴. All these disorders may constitute a rare and extreme derailment of BCSSS. EEG manifests with abundant and often continuous high amplitude sharp waves morphologically similar to the centrotemporal spikes and occipital paroxysms. Seizures are predominantly nocturnal and often resemble rolandic seizures. Otherwise typical rolandic epilepsy²⁵, Panayiotopoulos syndrome^{117,118} evolve to clinical and EEG features of epileptic encephalopathy of CSWS including Landau-Kleffner syndrome and atypical partial epilepsy of childhood¹⁸⁵. Atypical benign partial epilepsy of childhood probably is of intermediate severity between the epileptic encephalopathy of CSWS and BCSSS. The reason for this derailment of BCSSS is unknown, but may be related to location, epileptogenic threshold and other intrinsic and external superimposed factors. Intense epileptic activity in the dominant temporal region would affect linguistic capabilities as in Landau-Kleffner syndrome¹⁸⁶. Conversely, the mainly frontal localisation of CSWS primarily affects higher cognitive and executive functioning^{184,187,188}.

BCSSS and idiopathic generalised epilepsies

The majority of BCSSS if properly diagnosed do not have any clinical or EEG resemblance to idiopathic generalised epilepsies though others may disagree⁸⁴. Overlap of BCSSS with IGE is limited (see above). However, a possible link, the type and extent of which should be explored further with clinical and genetic studies may be suggested by:

- (a) the occurrence of EEG generalised discharges in BCSSS (though these are markedly different from the classical generalised spike or polyspike discharges of IGE) and
- (b) an undetermined but probably small proportion of patients with any type of BCSSS that may also suffer typical generalized convulsive or absence seizures either during the active phase of BCSSS or more often at a later stage
- (c) an undetermined but probably small proportion of patients with syndromes of IGE including childhood absence epilepsy that may also have focal spikes or typical seizures of BCSSS^{38,62,84}.

Management of benign childhood focal seizures

Short- and long-term treatment strategies of benign childhood focal seizures are empirical. In the acute stage, control of the seizure is paramount. On the rare occasions that the child is febrile, treatment of the underlying illness is also important. Long-lasting convulsive seizures

(>10 minutes) or convulsive status epilepticus (>30 minutes), although rare, constitute a genuine paediatric emergency that demands appropriate and vigorous treatment – as for prolonged febrile seizures and febrile status epilepticus. Benzodiazepines, in intravenous, rectal or buccal preparations, are used to terminate status epilepticus. Early parental intervention is more effective than late emergency treatment. Autonomic status epilepticus needs thorough evaluation for proper diagnosis and assessment of the neurological/autonomic state of the child. Aggressive treatment should be avoided because of the risk of iatrogenic complications⁸³.

Continuous antiepileptic medication is not usually recommended. Although there are effective therapies that could prevent the occurrence of additional seizures, potential adverse effects may not commensurate with the benefit. The risks of recurrent seizures are small, the potential side effects of drugs appear to outweigh the benefits and there is no convincing evidence that any therapy will alleviate the possibility of recurrences.

Decisions on management must take into account the following:

- (a) Most children have excellent prognosis: 10–30% may have only a single seizure and 60–70% may have less than 10 in total. However, 10–20% of children may have frequent seizures, which are sometimes resistant to treatment.
- (b) Remission of benign childhood focal seizures is expected in all patients by the age of 15–16 years at the latest.
- (c) There is no evidence that the long-term prognosis is worse in untreated children, although they may not be protected against seizure recurrences.
- (d) Some children become frightened, even by simple focal seizures, and some parents are unable to cope with the possibility of another fit despite firm reassurances.
- (e) Persistence and frequency of EEG functional spikes do not predict clinical severity, frequency or degree of liability to seizures.
- (f) In contrast to the other phenotypes of BCSSS, patients with ICOE-G often suffer from frequent seizures and therefore prophylactic AED treatment may be mandatory.

Secondarily GTCS are probably unavoidable without medication. Continuous prophylaxis consists of daily monotherapy using any AED that has proven efficacy in focal seizures. Most authorities recommend carbamazepine though this drug may exaggerate seizures in a minority of children with BCSSS including PS¹¹⁹. Recently, sulthiame has been revived as an excellent drug for the treatment of benign childhood epilepsy with centrotemporal spikes with EEG normalisation^{189,190} but this may be associated with cognitive abnormalities¹⁹¹. Of the newer drugs, levetiracetam has been reported as effective and safe^{192,193,66}. Lamotrigine on rare occasions may cause seizure exacerbation and cognitive deterioration¹⁹⁴.

When to withdraw medication differs among experts, although all agree that there is no need to continue with AEDS 1–3 years after the last seizure and certainly not after age 14 when most benign childhood focal seizures remit or 16 when they are practically non-existent.

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Table 1. Main features of rolandic epilepsy, Panayiotopoulos syndrome and idiopathic childhood epilepsy of Gastaut.

	Rolandic epilepsy	Panayiotopoulos syndrome	Idiopathic childhood occipital epilepsy of Gastaut
Prevalence amongst children aged 1-15 years with non-febrile seizures	15%	6%	0.5-1%
Peak age at onset	7-10 years	3-6 years	8-11 years
Male to female ratio	1:5	1	1
Seizure characteristics			
Typical onset with	Hemifacial sensory-motor or oropharyngolaryngeal symptoms	Autonomic symptoms mainly with emesis	Visual symptoms mainly with elementary visual hallucinations
Hemifacial sensory-motor symptoms	Common and often from onset	Rare and not from onset	Rare and not from onset
Oropharyngolaryngeal symptoms	Common and often from onset	Rare and not from onset	Have not been reported
Speech arrest	Common and often at onset	Rare and not from onset	Has not been reported
Hypersalivation	Common and often at onset	Rare and not from onset	Has not been reported
Ictus emeticus	Scarce and not from onset	Common and often at onset	Rare and not from onset
Autonomic disturbances other than vomiting and hypersalivation	Scarce and not from onset	Common and often at onset	Scarce and not from onset
Visual symptoms	Have not been reported	7% but exceptionally at onset	Common and often at onset
Deviation of the eyes	Frequent during sensory-motor symptoms	Common and may be at onset	Common but rarely at onset
Ictal behavioural disturbances	Scarce and not from onset	Common and often at onset	Have not been reported
Duration for 1-3 minutes	As a rule	Rare	As a rule
Duration of more than 5 minutes	Rare	Common	Rare
Partial status epilepticus (>30 min)	Exceptional	40%	Exceptional
Total number of seizures 1-15	As a rule	As a rule	Rare
Single seizures only	10-20%	30%	Exceptional

Table 1. (Continued)

	Rolandic epilepsy	Panayiotopoulos syndrome	Idiopathic childhood occipital epilepsy of Gastaut
Frequent seizures	10%	10%	90%
Nocturnal (sleep only)	70%	64%	Exceptional
Febrile convulsions	10–20%	17%	10%
Prognosis	Excellent	Excellent	Uncertain
Remission within 1–2 years from first seizure	Common	Common	Scarce or rare
Seizures after the age of 13 years	Rare	Scarce	Common
Inter-ictal EEG			
Centrottemporal spikes alone	As a rule and characteristic	Rare	Have not been reported
Occipital spikes	Have not been reported	65%	100%
Spikes in other locations	Probably uncommon	Frequent	Scarce
Brief generalised discharges of 3–5 Hz slow waves with small spikes	5%	10%	Exceptional
Somatosensory evoked spikes	Common	Rare	Have not been reported
Fixation-off sensitivity	Has not been reported	Common	Common
Photosensitivity	Has not been reported	Exceptional	Common
Normal EEG or focal slow wave after first seizure	-10%	-10%	-10%
Ictal EEG			
Ictal onset	Slow activity with spikes	Slow activity with spikes	Fast spikes and fast rhythms
	Rolandic regions	Anterior or posterior regions	Occipital regions

CHAPTER 10

The significance of the syndromic diagnosis of the epilepsies

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Classification of epileptic syndromes and diseases

Medical diagnosis is defined as:¹

'The identification of a disease by investigation of its symptoms and history, which provides a solid basis for the treatment and prognosis of the individual patient'.

The most significant advance in modern epileptology has been the recognition of epileptic syndromes and diseases, which provides a proper medical diagnosis for patients with epileptic disorders^{2–6}. The inclusive term 'epilepsy' is unacceptable because such generalisation defies diagnostic precision, which is the golden rule in medicine⁵.

'Epilepsy' is not a single disease entity. Epilepsies are hundreds of diseases with different causes, natural histories and prognoses, requiring different short-term and long-term management. Using the inclusive diagnostic label of 'epilepsy' instead of a precise seizure and syndrome categorisation endangers patients with epileptic seizures both medically and socially⁵. It is medically incorrect to label a child with temporal lobe epilepsy and a child with childhood absence epilepsy as simply having 'epilepsy' just because they both have seizures. This is as unsatisfactory as giving a diagnosis of 'febrile illness', irrespective of whether this is due to influenza, tuberculosis, bacterial meningitis, collagen disease, or malignancy.

Despite significant progress in the diagnosis and management of epilepsies, there are many reports in which patients with epileptic seizures are erroneously categorised as having 'epilepsy'. This situation has to change. Patients with epileptic seizures and their families are entitled to a diagnosis, prognosis, and management that is specific and precise.

In addition, new antiepileptic drugs (AEDs) are predominantly tested in partial epilepsies and inappropriate generalisations may be made about their use in other epilepsies such as idiopathic generalised epilepsies (IGE). The clinical significance of this is clearly demonstrated by vigabatrin and tiagabine, two of the new generation drugs for partial epilepsies. Both are potent drugs that induce absence seizures and absence status⁷. As such, they are contraindicated in IGE which make up one-third of 'epilepsy' cases⁵ yet this fact is not even mentioned in the British National Formulary on 'The control of epilepsy'. Many patients with IGE are treated incorrectly with these drugs as a result of such generalisations. Identification of the type of epilepsy is of utmost clinical importance, especially as satisfactory diagnostic precision is possible even after the first recognisable seizure⁸.

Seizure/symptom diagnosis

Accurately identifying the type(s) of seizures involved is the first, and not the final, step towards medical diagnosis in a patient with genuine epileptic seizures:

'An epileptic seizure is defined as an abnormal paroxysmal discharge of cerebral neurones sufficient to cause clinically detectable events that are apparent to the subject, an observer, or both'⁹.

This definition ranges from the dramatic event of a generalised tonic-clonic seizure to the mild myoclonic flicker of the eyelids or a focal numbness of the thumb and mouth. The latter are often overlooked although they are more important than generalised tonic-clonic seizures in the diagnosis of epilepsy⁶. Patients may often suffer many minor seizures long before or after their 'first seizure' or 'last seizure'⁶.

Epileptic seizures are classified¹⁰ as:

- *Generalised seizures* (tonic, clonic or tonic-clonic, myoclonic, typical or atypical absences)
- *Partial seizures* (with great variation in clinical expression and severity)
- *Partial seizures with secondary generalisation* (any partial seizure which progresses to become generalised).

Such a classification is necessary because 'an abnormal paroxysmal discharge of cerebral neurones' may be localised (partial seizures) or simultaneously affect the whole cerebral cortex from onset to termination (generalised seizures). Secondary generalised seizures are partial at onset but do not remain localised - they spread and trigger a generalised fit. Generalised seizures vary considerably: mild or severe myoclonic jerks; inconspicuous or severe typical and atypical absences; generalised clonic, tonic, tonic-clonic or clonic-tonic-clonic convulsions.

Symptom/seizure diagnosis cannot provide guidance to the physician on important items such as severity of the disease, prognosis, short and long-term therapeutic decisions, genetics (research and counselling) - all factors which crucially affect family and social life, and the education and career choices of patients. Precise syndromic diagnosis is necessary to ensure optimal management and avoid morbidity².

Syndrome/disease diagnosis

The diagnosis 'epilepsy' is no more precise than the term 'seizure' and similar arguments weigh against its use⁶. The World Health Organization Dictionary of Epilepsy¹¹ gives this definition:

'Epilepsy is a chronic brain disorder of various aetiologies characterised by recurrent seizures due to excessive discharge of cerebral neurones (epileptic seizures), associated with a variety of clinical and laboratory manifestations). Single or occasional epileptic seizures (such as febrile convulsions and the seizures of puerperal eclampsia) as well as those occurring during an acute illness should not be classified as epilepsy'.

Others consider epilepsy as a 'condition in which more than one non-febrile seizure of any type has occurred at any time'⁹. The statement: 'Epilepsy is two or more seizures' epitomises the current formal definition of the Commission on Classification and Terminology of the International League Against Epilepsy² and this does not even clarify what type of seizures. Such broad operational

definitions reveal the diagnostic inadequacy of the term 'epilepsy', which includes any patient with 'two undefined seizures' ranging from a normal child with two Rolandic seizures to the severely brain-damaged patient with daily multiform epileptic seizures. The recognition of epileptic syndromes and diseases, most of which are well defined and easy to diagnose, offers a clearly more precise and useful picture:

'An epileptic syndrome is a cluster of seizures, other symptoms, physical signs and laboratory findings, which are associated in a non-fortuitous manner'².

Identification of an epileptic syndrome requires clinical findings (type of seizure(s), age at onset, precipitating factors, severity and chronicity, circadian distribution, aetiology, anatomical location and prognosis) and data from ancillary studies (EEG, brain anatomical and metabolic imaging, haematology and biochemistry).

'A disease (as opposed to a syndrome) has common aetiology and prognosis despite variations in expression between individuals'².

In the current Classification of the International League Against Epilepsy (ILAE)² there are two major dichotomies/divisions:

- Whether the predominant seizure type is *localised* (localisation-related epilepsies and syndromes) or *generalised* (generalised epilepsies and syndromes), and
- Whether the aetiology is *idiopathic* (with a genetic predisposition, normal physical signs and development), *symptomatic* (structural), or *cryptogenic* (supposed of symptomatic, i.e. structural, cause but not demonstrable on MRI).

The combination of these divisions shapes the first two major groups of epileptic syndromes and diseases. A third group covers syndromes with seizures of uncertain focal or generalised nature, often the case in nocturnal seizures. The fourth and final group refers to syndromes where the seizures are related to a specific situation like fever, drugs or metabolic imbalance².

There is a long list of syndromes in each of the major divisions. Table 1 shows the syndromic classification of the generalised epileptic syndromes. Most syndromes start at an early age and there are profound differences in prognosis between syndromes with similar seizure/symptom diagnosis².

This classification² is not infallible: syndromes may overlap or evolve from one to another, syndrome definitions maybe inadequate, terminology may difficult or inappropriate and classification is sometimes complex. Such problems should pose a challenge to arrive at the proper medical diagnosis, and should not be used as an excuse against making one. Many of the proposed diseases/syndromes are common, well defined and easy to diagnose, such as juvenile myoclonic epilepsy¹². In some diseases/syndromes, like benign familial neonatal convulsions, genetics and pathophysiology have been dramatically clarified^{13,14}. Others, like the syndromes of idiopathic generalised epilepsy (IGE) with typical absence seizures^{15,16}, need further research and understanding for a better categorisation. Molecular genetics is already making decisive discoveries in the identification of epilepsies; new single-gene syndromes of partial epilepsy, like autosomal dominant nocturnal frontal lobe epilepsy, are now well documented^{17,18}.

If a syndromic/disease diagnosis is not possible, a symptom/seizure categorisation should be used and seizure type(s) should be clearly defined. A tentative disease/syndrome diagnosis should be used in conjunction with the seizure categorisation, and serve as basis for monitoring the natural history.

Table 1. Classification of generalised epilepsies and epileptic syndromes².

2.1	Idiopathic generalised age-related
2.1.1	Benign neonatal familial convulsions
2.1.2	Benign neonatal convulsions
2.1.3	Benign myoclonic epilepsy in infancy
2.1.4	Childhood absence epilepsy (pyknolepsy)
2.1.5	Juvenile absence epilepsy
2.1.6	Juvenile myoclonic epilepsy (impulsive petit mal)
2.1.7	Epilepsy with grand mal (generalised tonic-clonic) seizures on awakening
2.1.8	Other generalised idiopathic epilepsies not defined above
2.1.9	Epilepsies with seizures precipitated by specific modes of activation
2.2	Cryptogenic or symptomatic generalised
2.2.1	West syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe)
2.2.2	Lennox-Gastaut syndrome
2.2.3	Epilepsy with myoclonic-astatic seizures
2.2.4	Epilepsy with myoclonic absences
2.3	Symptomatic generalised
2.3.1	Non-specific aetiology
2.3.1.1	Early myoclonic encephalopathy
2.3.1.2	Early infantile myoclonic encephalopathy with suppression burst
2.2.1.3	Other symptomatic generalised epilepsies not defined above
2.3.2	Specific syndromes
2.3.2.1	Specific diseases in which seizures are the presenting feature

The significance of specifying the type of ‘epilepsy’

The significance and the challenges of the syndromic classification of epilepsies is exemplified by three common epileptic syndromes: benign childhood seizure susceptibility syndromes, juvenile myoclonic epilepsy and syndromes of temporal lobe epilepsy that comprise more than 40% of all epilepsies. They are entirely different in presentation, cause and genetics, investigative procedures, short and long-term treatment strategies and prognosis.

Benign childhood seizure susceptibility syndromes

Benign childhood seizure susceptibility syndromes (BCSSS) are detailed in Chapter 9. They comprise one-quarter of all childhood epilepsies. Like febrile convulsions, BCSSS are age-related, show genetic predisposition, may be manifested by a single seizure, remit within a few years of onset, and may or may not require a short course of antiepileptic medication. The risk of recurrent seizures in adult life (1–2%) is less than in febrile convulsions (4%). Recognition of the characteristic clinical and EEG features of BCSSS enable parents to be reassured of the invariably benign prognosis with spontaneous resolution of the disorder by the mid-teens^{6,19}.

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME) is an idiopathic generalised epileptic syndrome with distinctive clinical and EEG features^{12,20,21}. Prevalence is 8–10% among adult patients with seizures^{12,20,21}. It is characterised by myoclonic jerks on awakening, generalised tonic-clonic seizures, and typical absences, which occur in around one-third of patients. Seizures have an age-related onset. Myoclonic jerks are the defining seizures starting in the mid-teens and occurring mainly on awakening, particularly after sleep deprivation. The tendency to seizures is probably life-long. The management of JME differs from standard medical practice for the treatment of ‘epilepsy’ in several important respects^{20,21}.

An editorial in the Lancet by Grunewald and Panayiotopoulos in 1992 states the following^{12,21}: ‘There is no better example of the importance of syndrome classification than juvenile myoclonic epilepsy. JME accounts for between 5.4% and 10.2% of cases of epilepsy, but, despite clinical and electroencephalographic features that should enable its easy identification, the rate of misdiagnosis remains high. Accepted practice for management of ‘epilepsy’ will often be inappropriate in this condition - e.g. the withholding of treatment in patients who have had a single generalised tonic-clonic seizure, drug withdrawal after two or three years’ freedom from seizures, and stopping sodium valproate or substituting carbamazepine in women who plan to become pregnant. Accurate diagnosis does more than improve patient management and well-being; it also allows proper advice on prognosis, genetic risk, and employment. Failure to diagnose JME represents a serious medical error; how can diagnostic accuracy and management be improved? Physicians should be ever alert to the possibility of JME²¹.

The syndromes of temporal lobe epilepsy

The syndromes of temporal lobe epilepsy comprise more than 30% of epilepsies. They are a heterogeneous group of disorders sharing the same topographic seizure onset but often of diverse aetiology, age at onset, prognosis, response to medical or surgical management. Aetiology may be symptomatic, idiopathic or metabolic. The commonest of all, hippocampal epilepsy, is found in around 20% of patients with epilepsies. Hippocampal epilepsy is a distinct epileptic disease with defined pathology (hypocellular and gliotic ‘sclerotic’ hippocampus with a unique pattern of cellular loss, not found in other brain diseases). High-resolution magnetic resonance imaging (MRI) identifies existing pathology in around 90% of patients. Drug treatment is similar to other partial seizure types. Carbamazepine and phenytoin are the most effective of the older drugs. Of the newer drugs, all claim efficacy: lamotrigine, vigabatrin, topiramate, tiagabine, gabapentin, zonisamide. These treatments may be relatively effective in 80% of patients. If one or two of the main drugs fail, the chances of achieving medical control are negligible. These patients, even in childhood, need urgent evaluation for neurosurgical treatment for which they are the best candidates and the most likely to have excellent and sustained benefit²².

Epilepsy or epilepsies? Is this controversial?

Even the most sceptical physicians who doubt the clinical or practical significance of the syndromic diagnosis of epilepsies have to accept that BCSSS, JME and syndromes of temporal lobe epilepsy have more differences than similarities. They all require different management and their short and long-term treatment strategies are entirely different. What may be the best drug for one may be deleterious for the other.

The time is right for eradicating the traditional diagnostic label of ‘epilepsy’. This change may favourably influence the diagnosis, management, and welfare of people with epileptic seizures. The treatment of epilepsies will change but their correct diagnosis will always be the medical target. This concept is not difficult to understand and need not be controversial.

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CHAPTER 11

Idiopathic / genetic generalised epilepsies

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Introduction

The idiopathic generalised epilepsies (IGE), now often referred to as genetic generalised epilepsies (GGE), constitute roughly one-third of all epilepsies. Etymologically, the term 'idiopathic' comes from the Greek word 'idios', which simply means 'oneself'. An idiopathic syndrome therefore may be conceptualised as a disease unto itself, a *sui generis* condition. It follows that an idiopathic epilepsy syndrome:

- Consists only of recurrent epileptic seizures
- Is not associated with structural brain lesions on MRI or abnormal neurological symptoms and/or signs inter-ictally and implies normal neuropsychological status.

It should be also made clear that the term idiopathic is not synonymous with 'benign', as some subtypes such as juvenile myoclonic epilepsy (JME) are often life-long conditions, or with 'genetic', as not all genetic conditions are idiopathic, such as the progressive myoclonic epilepsies, or finally with 'unknown aetiology', as the genetic background of some subtypes such as JME and childhood absence epilepsy (CAE) has already been identified¹.

The term 'generalised' refers to the seizures 'in which the first clinical changes indicate initial involvement of both hemispheres... The ictal encephalographic patterns initially are bilateral'^{2,3}. This statement however is not entirely true. Video-EEG experience has taught us that typical absences (TA) may show an interhemispheric difference of 100-200 ms at their onset (without consistent side emphasis), and that some patients may show focal or lateralising ictal clinical features^{4,5}. Finally, at least 40% of patients with idiopathic generalised epilepsies (IGE) display non-localising focal discharges in the inter-ictal EEG (with or without generalised discharges)⁴⁻⁶.

The IGEs comprise several sub-syndromes, characterised by all or some of the three seizure types - TA, myoclonic jerks and generalised tonic-clonic seizures (GTCS) - in different combinations and emphasis. These sub-syndromes usually have distinct electroclinical features and prognosis; some are life-long while others are age-related. However, accurate syndromic diagnosis may not be possible from the first presentation, and a number of patients with IGE may be difficult to classify.

The classification of IGE sub-syndromes over recent years has been controversial and a lively debate continues in view of the long-awaited new classification scheme of the ILAE⁷. There are two schools of thought: the 'lumpers', who hold that although IGE sub-syndromes can be recognised, their boundaries are indistinct, and that all forms of IGE fall into the same neurobiological continuum with genetic relationships^{8,9}; and the 'splitters', who take the view that precise syndromic classification provides a nosologic framework of utmost importance for treatment and prognosis of an individual patient, and a sound basis for genetic and neurobiological research¹⁰⁻¹².

The Commission on Classification of the ILAE³ defined IGE as follows:

Idiopathic generalised epilepsies are forms of generalised epilepsies in which all seizures are initially generalised (absences, myoclonic jerks and generalised tonic-clonic seizures), with an EEG expression that is a generalised bilateral, synchronous, symmetrical discharge (such as is described in the seizure classification of the corresponding type). The patient usually has a normal inter-ictal state, without neurological or neuroradiologic signs. In general, inter-ictal EEGs show normal background activity and generalised discharges, such as spikes, polyspike spike-wave, and polyspike-waves³ 3 Hz. The discharges are increased by slow sleep. The various syndromes of idiopathic generalised epilepsies differ mainly in age of onset. No aetiology can be found other than a genetic predisposition towards these disorders.

The seizures in IGE

The seizures of IGE are TA, myoclonic jerks and GTCS^{2,3}. Of these, TA occupy a central position as they occur almost exclusively in the context of the IGEs², and are neurophysiologically and pharmacologically unique^{13,14}, which in turn makes their treatment different.

1. Typical absences

TA are brief, generalised epileptic seizures, characterised clinically by impairment of consciousness (absence) that occurs without warning and also ceases suddenly and without post-ictal symptoms, and electrographically by generalised 4–3 Hz spike and slow-wave discharge² that terminates without subsequent electrical flattening. Along these rather strict lines, TA tend to display a considerable clinical and EEG variability that may be syndrome-related.

Impairment of consciousness may range from mild to severe, and may occur either in isolation, or in association with other ictal manifestations, such as automatisms, autonomic signs, and regional (mouth or eyes) or widespread (head, limbs, and trunk) rhythmic or random myoclonia. Clinical subtypes of TA therefore include absences with impairment of consciousness only, with clonic, atonic, tonic, or autonomic components, and with automatisms^{2,15,16}. In turn, the accompanying EEG discharge may be very brief or long (usually between 3 and 30 seconds), continuous or fragmented, with regular or varying intradischarge frequency, may display spike or multiple spike components, and even show non-consistent side preponderance. It is usually faster and unstable in the opening phase (first second), becomes more regular and stable in the initial phase (next three seconds), and slows down towards the terminal phase (last three seconds). Background activity is normal, and inter-ictal fast, non-localising spikes may occur, usually over the frontal areas.

TA may occur spontaneously, and are typically provoked by hyperventilation, but also by other specific triggers, e.g. photic or pattern stimulation, video games, thinking, or even reading. They may be the sole or the predominant seizure type in individual patients, such as in CAE or juvenile absence epilepsy (JAE), or coexist with other generalised seizures, such as GTCS or myoclonic jerks, as in JME. Natural history may also vary: TA may remit with age or persist requiring continuous treatment; approximately 10–15% of adults with epilepsies have TA, often combined with other types of generalised seizures^{17–19}.

A distinction should be made between typical and atypical absences. As opposed to TA, atypical absences² occur only in the context of mainly severe symptomatic or cryptogenic epilepsies of children with learning difficulties, who also suffer from frequent seizures of other types such as atonic, tonic, and myoclonic seizures. Clinically, onset and offset may not be as abrupt as in TA, and ictal changes of tone are usually more pronounced. The EEG features are also different: the ictal discharge is slower (<2.5 Hz) and irregular, and may include other paroxysmal activity. Background activity is usually abnormal, and consistent focal abnormalities may exist.

2. Myoclonic seizures

Myoclonic seizures (MS) are shock-like, brief, irregular, arrhythmic and less often rhythmic, clonic twitching movements singular or repetitive^{2,3}. They may affect facial, limb, and neck or trunk muscles with varying force, amplitude and combinations. Their force may range from mild and inconspicuous movements of the affected muscle groups to violent movements of limbs and body that may make the patient fall on the ground, drop or throw things or kick in the air. Commonly, the same patients experience combinations of mild and violent jerks. MS may affect any muscle or group of muscles. They predominantly affect eyelids, facial and neck muscles, and the upper more than the lower limbs. MS of IGE occur mainly on awakening. Precipitating factors include sleep deprivation, fatigue, excitement or distress, and often photic stimulation.

In pure MS consciousness is not impaired and the patient is fully aware of them. However, myoclonic jerks are often a consistent ictal symptom of absence seizures^{20,21}. The EEG hallmark of MS are generalised bursts of polyspikes/polyspike-wave with variable side emphasis and anterior predominance.

Eliciting a clinical history of MS is not always straightforward. The answer to a direct question ‘Do you have jerks?’ is usually negative. Diagnostic yield improves by physically demonstrating myoclonic jerks, and by inquiring about morning clumsiness and tremors (‘Do you spill your morning tea?’ or ‘Do you drop things in the morning?’). Demonstrating that MS often relate to fatigue, alcohol indulgence and sleep deprivation is also essential. One has to bear in mind that MS may not be perfectly symmetrical and that occasionally they may be clearly lateralised, although without consistent side emphasis.

3. Generalised tonic-clonic seizures

GTCS in IGE are primary in the sense that they are generalised from onset as opposed to the secondary GTCS in focal epilepsies. The seizure itself is the same irrespective of epilepsy syndrome. The main difference is in the preceding and sometimes in the ensuing clinical and EEG phases. The GTCS in focal epilepsies are secondary to a cortical focus and may be preceded by subjective symptoms (aura) or signs that indicate a focal onset. Post-ictal lateralising electroclinical features (such as more depressed EEG activity over one hemisphere or asymmetry in muscle hypotonia) would also argue for a focal onset. Conversely, GTCS in IGE will occur without initial focal features, either out of the blue or after clusters of MS or TA, or absence status epilepticus that may warn patients of an impending convulsion. However, one has to bear in mind that rapid secondary generalisation may effectively conceal a focal or lateralising onset from a symptomatic focus, and conversely that GTCS in IGE may occasionally start with focal features such as head turning.

Though dramatic, GTCS do not bear any diagnostic significance. It is the minor seizures that provide the clues to diagnosis, investigative procedures and appropriate management. Patients often seek medical attention for the first time because of a GTCS. This is often erroneously considered as the ‘first seizure’ and is not treated or investigated. The truth is that the first GTCS in IGE is usually preceded for months or years by undiagnosed MS and TA, and it is their recognition that should prompt suitable treatment. Conversely, patients may not have GTCS for years, but this does not necessarily mean that they are ‘seizure free’. Absences or myoclonic jerks may continue, and treatment should be optimised instead of withdrawn.

The syndromes of IGE / GGE

Epilepsy syndromes, defined as clusters of symptoms or signs occurring consistently together, form the basis of the currently accepted classification of the epilepsies, and such a concept is practical for diagnosis, orientation of treatment and prognosis, and selection of appropriate investigations. A number of IGE syndromes feature in the current³ and the recently proposed⁷ classification systems of the ILAE, while others have not been recognised yet. In addition, there are patients with IGE who do not fit easily into recognisable syndromes.

The IGE / GGE syndromes currently recognised by the ILAE are shown in Table 1. Benign neonatal familial convulsions, benign neonatal convulsions and benign myoclonic epilepsy in infancy are not dealt with here.

IGE syndromes not yet recognised by the Commission of the ILAE include eyelid myoclonia with absences (EMA), perioral myoclonia with absences (PMA), idiopathic generalised epilepsy with phantom absences, and stimulus-sensitive absence epilepsies.

Childhood absence epilepsy (CAE)^{12,20,22} is the archetypal syndrome of typical absence seizures, with onset usually before the age of ten years and a peak at 5–6 years. The prevalence of CAE is 10–12% for children with epilepsy younger than 16 years of age^{23,24}. As a rule, TA is the only seizure type at presentation and for the first active period of absences, but infrequent GTCS may occur in adolescence or adult life. TA occur frequently (tens or hundreds per day), last for 4–30 seconds (usually around 10 seconds), and are associated with severe impairment of consciousness.

Clinically, there is abrupt and severe loss of awareness, and complete unresponsiveness. The eyes spontaneously open and stare or move slowly, and all voluntary activity stops within the first 3 seconds of the seizure. Random eyelid blinking (usually not sustained) may occur, and mild, mainly orofacial, automatisms are frequent¹⁵. There may also be a transient impairment of postural tone, resulting in the head, limbs or trunk dropping, and sometimes an increase in tone that leads to retropulsion. Ictal clinical symptoms and signs inconsistent with CAE include mild impairment of consciousness, pronounced and rhythmical myoclonus either regional (eyelid or perioral) or massive limb jerking, and single or arrhythmic myoclonic jerks of the head, trunk, or limbs. The occurrence of other generalised seizures, such as GTCS, or myoclonic jerks, prior to or during the active period of the absences, and sensitivity to photic or other sensory triggers is also thought to be incompatible with CAE^{12,20,22}. The background EEG is normal with frequent rhythmic posterior delta activity. Ictal discharges consist of generalised high amplitude 2.5–4 Hz spike-wave and are longer than 4 seconds.

Prognosis and evolution of CAE depends on the applied diagnostic criteria. Delineated as above, CAE has an excellent prognosis; TA are responsive to treatment and remission occurs in more than 80–90% of children before the age of 12 years. However, prognosis becomes variable when one includes in CAE every child with onset of absences before the age of ten years. GTCS occur in perhaps more than one-third of patients, either during adolescence²⁵ or in the third decade of life²⁶, and some patients may develop JME^{1,27}. TA in these patients may persist, improve or disappear. Most of the available evidence on the prognosis of CAE is inconclusive, and certainly one could argue that such patients may not have CAE but another form of IGE (JAE or JME).

Juvenile absence epilepsy (JAE)^{20,28,29} is mainly characterised by TA that are similar to those in CAE, but much less frequent and probably not as severe. Age at onset of TA is 7–16 years with a peak at 10–12 years. Random and infrequent myoclonic jerks^{15,30}, as well as infrequent GTCS, occur in most of the patients. One-fifth of patients also suffer attacks of absence status epilepticus³¹.

TA may be frequent, sometimes daily. The interrupted ongoing voluntary activity may be partly restored during the ictus, and clinical recovery may occur prior to the termination of the EEG ictal discharge. Automatisms are frequent, usually occurring 6–10 seconds after the onset of the discharge. The combination of peri-oral or hand automatisms and staring may lead to misdiagnosis of such TA for complex partial (limbic) seizure and vice versa⁶. JAE is usually a life-long disorder, but absences tend to become less severe with age. The ictal EEG is not fundamentally different than in CAE. Similarly, to the latter, ictal features such as mild impairment of consciousness and brief ictal discharges (less than 4 seconds), eyelid or perioral myoclonus, rhythmic limb jerking, and single or arrhythmic myoclonic jerks are thought to be exclusion criteria for JAE. As with CAE, 80% or more of the patients become seizure free with appropriate treatment, but the risk of relapse following discontinuation of medication is not clearly defined.

Table 1. Idiopathic generalised epilepsies as perceived by the relevant Committees of the ILAE.

Commission of the ILAE (1989)

Idiopathic generalised epilepsies

Benign neonatal familial convulsions

Rare, dominantly inherited disorders manifesting mostly on the second and third days of life, with clonic or apnoeic seizures and no specific EEG criteria. History and investigations reveal no aetiological factors. About 14% of patients develop epilepsy later.

Benign neonatal convulsions

Very frequently repeated clonic or apnoeic seizures occurring about the fifth day of life, without known aetiology or concomitant metabolic disturbance. Inter-ictal EEG often shows alternating sharp theta waves. No recurrence of seizures. Psychomotor development not affected.

Benign myoclonic epilepsy in infancy

Characterised by brief bursts of generalised myoclonus associated with generalised spike-waves occurring during the first or second year of life in otherwise normal children who often have a family history of convulsions or epilepsy. Generalised tonic-clonic seizures may occur during adolescence.

Childhood absence epilepsy (pyknolepsy)

Juvenile absence epilepsy

Juvenile myoclonic epilepsy (impulsive petit mal)

Epilepsy with generalised tonic-clonic seizures on awakening

Epilepsies with seizures precipitated by specific modes of activation
Most of the photosensitive epilepsies belong to the group of idiopathic generalised epilepsies.

Other generalised epilepsies not defined above

ILAE Task Force on Classification (2001)

Idiopathic generalised epilepsies

Benign myoclonic epilepsy in infancy

Epilepsy with myoclonic astatic seizures

Childhood absence epilepsy

Epilepsy with myoclonic absences

Idiopathic generalised epilepsies with variable phenotypes

Juvenile absence epilepsy

Juvenile myoclonic epilepsy

Epilepsy with generalised tonic-clonic seizures only

Generalised epilepsies with febrile seizures plus (to consider)

*Juvenile myoclonic epilepsy (JME) (Janz syndrome)*³² is characterised by myoclonic jerks on awakening, GTCS, and TA, with the latter occurring in more than one-third of the patients^{28,33,34}. However, TA are not the predominant seizure type, and are usually very mild and simple (with no automatisms or localised limb jerks). Seizure precipitating factors include sleep deprivation and fatigue, alcohol, and mental and psychological arousal, and up to 40% of patients are photosensitive³³. TA, when present, begin between the ages of five and 16 years, MS usually follow sooner or later, with the GTCS being the last to appear in most cases. An adult form of this syndrome has also been described³⁵. All seizure types are probably life-long, although TA may become less severe with age, and MS and GTCS commonly improve after the fourth decade of life. Prevalence of JME alone is around 9% of adults with seizures³⁴, and both sexes are equally affected. Generalised spike-wave discharges at 3–6 Hz have an unstable intradischARGE frequency with fragmentations and multiple spikes.

Myoclonic absence epilepsy (MAE) is a rare generalised cryptogenic or symptomatic absence epilepsy, although an idiopathic form may also exist. TA occur many times a day and constitute the predominant seizure type. Ictally, severe bilateral rhythmical clonic jerks are often associated with a tonic contraction, and some awareness is maintained. Age of onset is around seven years, and there is a male preponderance. Prognosis is not good because of resistance to therapy, mental deterioration, and possible evolution to other types of epilepsy such as Lennox-Gastaut syndrome^{36,37}.

Epilepsy with GTCS on awakening. The term denotes an idiopathic propensity to mainly or exclusively GTCS that occur mostly within the first two hours after awakening from sleep^{3,38,39}. They may also occur when the patient is awake at times of relaxation and leisure. Age at onset is mainly in the mid-teens but may start earlier or much later. Sleep deprivation, fatigue and excessive alcohol consumption are main precipitating factors. GTCS tend to increase in frequency with age and may become unpredictable occurring also during sleep and alert stages. Avoidance of precipitating factors and adjustment of lifestyle are essential for the best management of these patients.

There is a considerable overlap with other IGEs that also manifest a similar circadian distribution and precipitating factors. Idiopathic epilepsy with GTCS on awakening³ is no longer recognised as a separate syndrome⁷. Instead, this is now rightly considered as part of 'IGE with GTCS only', referring to all patients with GTCS only, irrespective of circadian distribution. There are no other discernible clinical seizures though video-EEG may often demonstrate 'phantom absences'.

The following syndromes are not recognised by the ILAE:

Eyelid myoclonia with absences (EMA). TA are frequent, typically associated with marked, rhythmic, and fast jerks of the eyelids, often with jerky upward deviation of the eyeballs and retropulsion of the head. Absences are brief (3–6 seconds) and occur mainly after eye closure. GTCS and random myoclonic jerks of the limbs may occur infrequently, most likely after sleep deprivation, fatigue, and alcohol intake. Marked photosensitivity is the rule but declines with age. EMA usually starts in early childhood but may be resistant to treatment. The ictal EEG manifestations consist mainly of generalised polyspikes and slow-waves at 3–6 Hz^{40,41}. Patients practising self-induction should be differentiated from pure EMA and treated accordingly.

Perioral myoclonia with absences (PMA). Here, TA are also frequent and usually brief, associated with a variable impairment of consciousness and rhythmic myoclonus of the perioral facial or masticatory muscles. Clusters of absences or absence status occur commonly and may precede GTCS. The latter are not frequent. PMA starts in childhood or early adolescence and TA and GTCS may be resistant to medication. Ictal EEG discharges are often irregular and consist of rhythmic multiple spike-waves and slow-waves at 3–4 Hz. Photosensitivity is not encountered^{42,43}.

Absences with specific modes of precipitation (photic, pattern, video-games, emotional upset, intense thinking, and reading) and their underlying mechanisms have been recently reviewed⁴⁴. Photosensitivity is estimated to occur in approximately one-fifth of patients with onset of absences in childhood or adolescence and it is associated with unfavourable prognosis. Apart from all patients with EMA and up to 30–40% of those with JME who are photosensitive, others with spontaneous and photically provoked absences and GTCS may belong to various syndromes not yet identified.

Two clinical - EEG phenotypes that are associated with episodes of absence status but are not included as IGE sub-syndromes in the official ILAE classification are described below.

Epilepsy with phantom absences (E-PA)

The key diagnostic feature and the defining seizure type is phantom absences (PA), the only type of absence in the EEG of mainly adults, who typically present with the first GTCS, or with an episode of absence status (AS) frequently culminating in a GTCS. There is no past history of absences or myoclonic jerks, including childhood and early adolescence. All patients have GTCS and half of them may have one or more episodes of AS that do not dominate the clinical presentation. Absences (apart from phantom) and myoclonic seizures are not part of this syndrome. Photosensitivity is rare. The syndrome is not self-limiting, but response to appropriate antiepileptic medication is satisfactory in most patients^{18,88}.

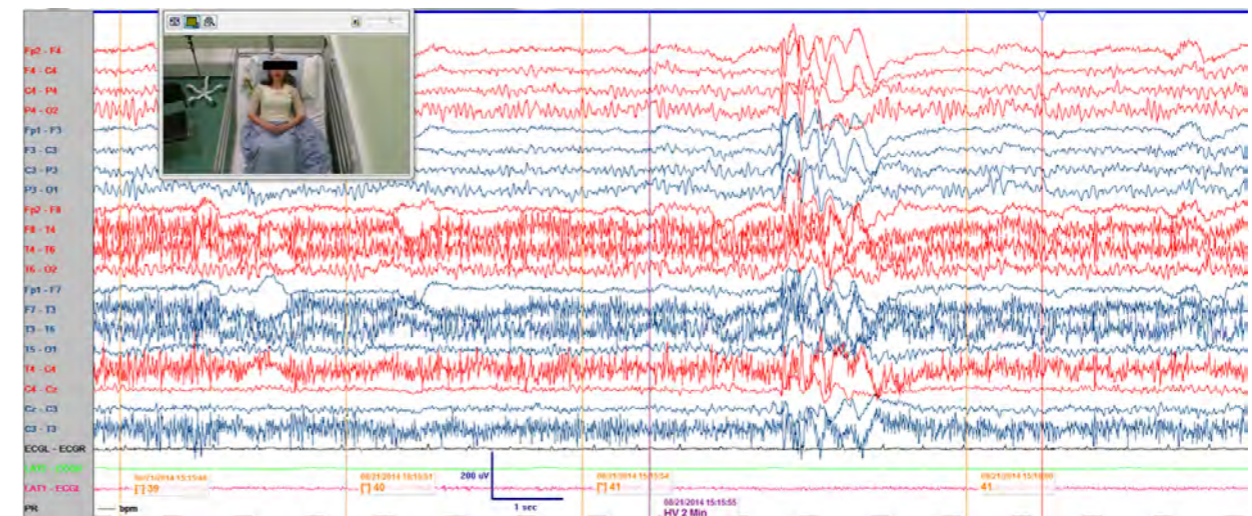


Fig 1: HV with breath counting in a 27-year-old woman with 3 GTCS in a space of 7 years. She had no history of absences, myoclonic jerks or long dyscognitive periods suggestive of absence status (AS). Note the hesitation in breath counting before repeating the same number, caused by a shorter than 2 seconds GSWD (phantom absence). She had no overt absences, while previous EEGs elsewhere had reported subclinical 3Hz GSWD.

Absence status epilepsy (ASE)

As the term indicates, ASE is characterized by recurrent, unprovoked episodes of absence status (AS), which is the predominant and defining seizure type for this syndrome. Most patients may have infrequent GTCS while few may have a history of, also infrequent, absences. Phantom absences and myoclonic seizures are not part of this syndrome, and photosensitivity has not been reported. In most patients the syndrome starts between adolescence and early to mid-adulthood and, although it is not self-limiting, response to appropriate antiepileptic medication is usually satisfactory⁹⁰. As in the epilepsy with PA, episodes of AS occur without provocation and are not merely due to the aggravating effects of inappropriate for GGE/IGE AED⁹¹.

Recurrent episodes of AS is the key diagnostic feature. The severity of clouding of consciousness ranges from very mild to severe (Figure 2). GTCS occur in most patients, either in association with an episode of AS (usually at the end), or independently; in some patients they may be the first overt clinical manifestation, but do not predominate the clinical presentation. Absences may occur in a few patients, either in childhood or later, but are infrequent and their whole clinical profile appears to resist classification into the two recognized absence syndromes of CAE or JAE.

Independent myoclonic seizures and phantom absences are not part of the syndrome⁹⁰.

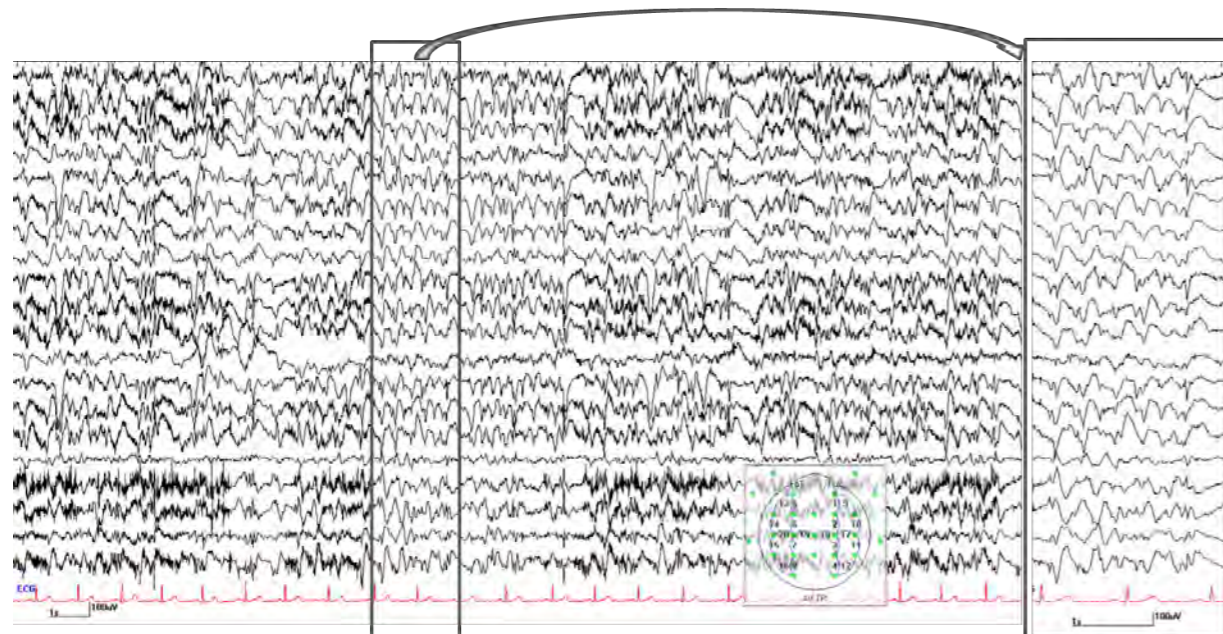


Fig 2: Video EEG showing AS in a 59-year-old woman with frequent attendances to the emergency department for episodes of prolonged confusion. Throughout this EEG, performed several hours after the onset of AS, she remained in a sitting position with her eyes open and was unresponsive to commands, though she seemed vaguely aware of the presence of people around her. She had some semi-purposeful movements and at times slight shaking of the hands and feet. Note the arrhythmic pattern of the generalized discharge, the frequency of which ranges from ≤ 2 Hz to 4Hz.

Absences in symptomatic or cryptogenic (probably symptomatic) focal epilepsies

Such absences have been documented only occasionally and in specific topographic and pathologic substrates, notably in patients with seizures arising from the medial intermediate frontal area⁴⁵, and in others with cerebral cortical dysgenesis and involvement of the archicortex⁴⁶. In both instances, brief impairment of cognition associated with 3 Hz spike-wave EEG paroxysms would probably qualify these seizures as TA, but these absence-like events usually coexist with complex partial seizures with or without secondary generalisation and require completely different management. TA may occasionally arise as a consequence of a known disorder of the central nervous system⁴⁷, but in most cases an aetiological link is not proven, and it is likely that they are coincidental. Finally, the co-existence of IGE with TA and symptomatic partial epilepsy in the same patient is seemingly rare although probably underdiagnosed⁶.

Diagnosis and differentials

Diagnosis of TA in children with severe ictal impairment of consciousness is relatively easy. Their brief duration with abrupt onset and termination, high daily frequency, and nearly invariable provocation

with hyperventilation makes them one of the easiest types of seizures to recognise. The child with suspected TA should be asked to overbreathe for three minutes, counting his or her breaths while standing with hands extended in front; hyperventilation will provoke an absence in more than 90% of those who suffer. We recommend that this test should also be undertaken in suspected adults, in whom TAs are usually mild and may be missed. Misinterpretation of TA for partial seizures (focal motor in the case of regional asymmetric ictal myoclonic components, or complex partial - limbic - when ictal automatisms, such as perioral, swallowing, fumbling are present) may seriously affect management and treatment. The basic clinical criteria for differentiating TA from complex partial seizures are given in Table 2. The clinical approach needs to be complemented by (preferably video) EEG studies, ideally prior to commencing treatment. An EEG would confirm the diagnosis of TA in more than 90% of these untreated children with ictal recordings mainly during hyperventilation. If not, the diagnosis of absences should be questioned⁴⁸. In addition, ictal video-EEG documentation may reveal features favouring a specific epileptic syndrome and assist in determining long-term prognosis and management. The fundamental EEG differences between TA and complex partial seizures are also shown in Table 2.

Diagnosis of other co-existent seizure types, and definition, if possible, of the electroclinical syndrome as outlined in the previous section is the final diagnostic step before initiating treatment. Symptomatic absences in non-lesional frontal lobe epilepsy are often impossible to distinguish, especially in the absence of partial seizures⁴⁵. Cerebral cortical dysgenesis is usually detectable on brain MRI⁴⁶. Such symptomatic/cryptogenic absences are very rare. Finally, TA in IGE can be easily differentiated from atypical absences that occur only in the context of mainly severe symptomatic or cryptogenic epilepsies in children with learning difficulties and frequent seizures of other types, such as atonic, tonic, and myoclonic seizures.

Treatment

General principles

Prognosis is syndrome-related. For instance, childhood absence epilepsy is a relatively benign syndrome, which usually remits within 2-5 years from onset. In all other IGE syndromes there is probably a life-long liability to TA, myoclonic jerks, and GTCS. Poor initial response to treatment^{49,50} and photosensitivity⁴⁹ may be of adverse prognostic value for long-term remission of seizures. Repeat EEG is particularly useful in monitoring the response to treatment as there is a very close correlation between control of clinical absences and electrographic abnormalities^{51,52}; such a relationship does not exist in other generalised seizures (tonic-clonic or myoclonic), or in partial epilepsies.

Planning of management and appropriate advice and counselling is therefore possible once a confident syndromic diagnosis has been established, or at least the question of possible photosensitivity or other reflex activation, and the co-existence of myoclonic jerks, GTCS or both has been answered satisfactorily. Currently, sodium valproate, ethosuximide and lamotrigine, alone or in combination, are the only first-line agents for TA. Choice between them depends on other co-existent generalised seizures, and - obviously - adverse reactions. Table 3 presents the proposed steps in the therapeutic process that targets TA in different clinical patterns.

Monotherapy

Satisfactory seizure control with monotherapy is the desired aim in the treatment of the epilepsies, and naturally IGE is not an exception. Any of the three first-line drugs can be initiated and lack of effectiveness should not be assumed before ensuring that the maximum tolerated dose has been achieved. If monotherapy with a particular agent finally fails, or unacceptable adverse reactions appear, substitution with one of the other drugs is the next step.

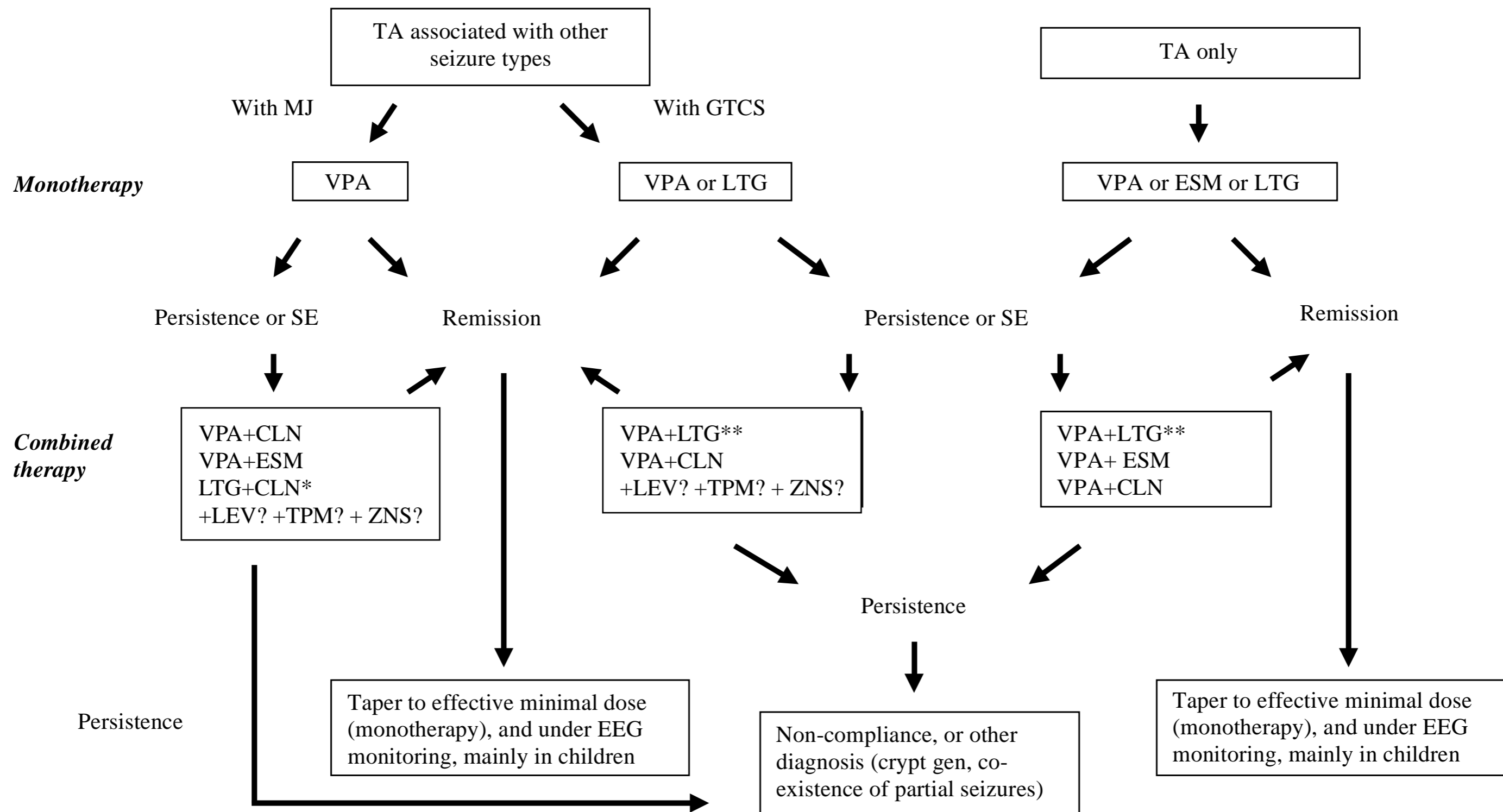
Table 2. Differential diagnosis between typical absences and limbic temporal lobe seizures.

History	Limbic CPS (mesial TLE)	Typical absences (IGE)
Febrile convulsions	Frequent; usually multiple, prolonged or complicated	Frequent but rarely prolonged or complicated
Family history	Usually of febrile convulsions; rarely of partial seizures (familial TLE)	Positive in up to 40% of patients
Onset	Usually within the second half of the first decade	Usually syndrome-related
Course (natural history)	Often bi-phasic	Continuous*
Diurnal variation	Non-specific	Usually in the morning/after awakening
Ictal clinical features		
Aura	Frequent	Never
Precipitation by HV	Exceptional	As a rule
Precipitation by IPS	Exceptional	Typical (but usually syndrome-related, as in JME and EMA)
Lapse of awareness	Usually profound	Varies (often syndrome-related)
Automatisms	Almost invariably, often involving trunk and legs. Ipsilateral to the focus automatisms associated with contralateral dystonic posture may occur in 40% of patients late in the seizure	Up to about 2/3 of seizures, rarely involving trunk or legs
Clonic components	Rare; unilateral - if present - and late in the ictal sequence	Frequent, bilateral, mainly restricted to the eyelids or mouth
Reactive automatisms	Frequent	Only during absence status
>1 min duration	As a rule	Exceptional
Non-convulsive status	Exceptional	Well recognised feature
Post-ictal symptoms/signs	Invariably confusion, recent memory deficit, dysphasia if onset from the dominant side. Relatively rapid clearing may occasionally occur	Never
Inter-ictal EEG (scalp)	Unilateral or bilateral independent temporal spikes, or regional slow activity. Brief bilateral and synchronous bursts of spike-wave may occur in the context of obvious or occult secondary bilateral synchrony	Generalised spike and wave discharges at 4–2.5 Hz. Focal spikes may occur in up to 30–40% of traces but they show frontal topography, and do not disturb background activity
Ictal EEG (scalp)	Focal onset	Generalised onset
Neurological examination	Normal (a degree of facial asymmetry may be present)	Normal
Neuropsychology	Often discrepancy between Verbal IQ and Performance IQ, material specific memory deficits	Normal
Brain MRI	Usually mesial temporal atrophy	Normal

HV: hyperventilation; IPS: intermittent photic stimulation;

*: in CAE GTCS may occur in up to 1/3 of patients after the remittance of the typical absences

Table 3. Tree diagram of the treatment of TA according to syndrome-related co-existence of other seizure types.



MJ: myoclonic seizures; GTCS: generalised tonic-clonic; VA: sodium valproate; ESM: ethosuximide; LTG: lamotrigine; CLN: clonazepam; LEV: levetiracetam; TPM: topiramate; SE: side effects; *: in VA-resistant or -sensitive patients (e.g. women), and probably when the myoclonic component is not severe; **: titrate the dose of LTG according to clinical response; low to moderate doses are usually effective; ?: effectiveness as adjunctive treatment remains to be proven

Sodium valproate is the most effective drug in the treatment of all types of generalised seizures with 75% of patients becoming seizure-free on monotherapy. It is used by most physicians not only as first choice for monotherapy irrespective of absence syndrome, but also as a solid basis for adjunctive therapy^{53,54} (Table 3). In addition, sodium valproate prevents the recurrence of absence status⁵⁵, is effective in myoclonic absences⁵⁶, which are particularly difficult to treat, and can abolish photosensitivity. There are anecdotal reports where children may not respond to the syrup form, despite adequate levels, but do so with sodium valproate tablets. Common adverse effects include nausea, vomiting, dyspepsia, gain in bodyweight, tremor, transient hair loss and haematological abnormalities. The latter, even when highly clinically significant, can be reversible following dosage reduction; discontinuation is rarely required⁵⁷. Behavioural and cognitive abnormalities, and acute liver necrosis⁵⁸ and pancreatitis, that may be fatal and more likely to occur in children on polypharmacy, are rare. However, the main factors that hamper its use, mainly in women⁵⁹, include an estimated risk of 1–2% for neural tube defects, predominantly spina bifida aperta, in pregnancy (background population risk 0.2–0.5%), which may increase when the drug is combined with benzodiazepines⁶⁰, the as yet unresolved question of polycystic ovarian syndrome^{61–63} and other endocrine side effects, and hair loss. Occasional worsening of TA with sodium valproate has been reported⁶⁴.

Ethosuximide is effective in TA, nearly as much as sodium valproate⁶⁵, but does not protect against GTCS and myoclonic seizures (Table 3). Therefore, while ethosuximide might be a reasonable choice in a young child with CAE, it is not recommended as a first-line choice in an older child with possible JAE (due to the much higher chance of developing CTCS), and in JME. Common adverse effects are usually dose-related and include gastrointestinal disturbances, anorexia, weight loss, drowsiness, photophobia and headache. Behaviour and psychotic disturbances may occur. Aplastic anaemia, Stevens-Johnson syndrome, renal and hepatic impairment are rare but life threatening.

Lamotrigine controls TA and GTCS^{66,67}, but its effect on MS is unpredictable (Table 3), and exacerbation of JME has been reported with lamotrigine⁶⁸. Lamotrigine monotherapy may be tried in women, particularly those that may be more vulnerable to side effects of sodium valproate. Dose escalation should be gradual: in adults and children over 12 years initial dose is 25 mg daily for two weeks, followed by 50 mg daily for two weeks. Maintenance dose is 100–200 mg/day in two divided doses but can be increased to 400 mg per day in the absence of a satisfactory response. In younger children, and in accordance with the recommendations regarding add-on lamotrigine in this age group, the initial dose is 0.3 mg/kg bodyweight/day daily for two weeks, followed by 0.6 mg/kg/day daily for two weeks. Maximum escalation should not exceed 0.6 mg/kg every 1–2 weeks until optimal response. Maintenance dose usually ranges between 2.5 and 7 mg/kg/day given in one or two divided doses but can reach 10 mg/kg/day if lamotrigine is not combined with sodium valproate. This gradual initial dose titration reduces the risk of allergic skin rash, which is higher when the drug is prescribed in combination sodium valproate which inhibits lamotrigine metabolism. Skin rash occurs in approximately 10% of patients, usually in the first eight weeks, and prompts discontinuation of the drug. Serious rashes leading to hospitalisation, including Stevens-Johnson syndrome and hypersensitivity syndrome, occur in approximately one in 300 adults and one in 100 children^{67,69}. Other common side effects include headache, nausea, diplopia, dizziness, ataxia and tremor.

Combined therapy and second-line anti-absence drugs

Selection of drug combination is again based on the clinical pattern principle.

Lamotrigine. More than half of patients with valproate-resistant absences may become seizure free with add-on lamotrigine⁷⁰. This combination is also highly effective with regard to myoclonic seizures and GTCS (Table 3). The effect is probably mediated through inhibition of lamotrigine metabolism by sodium valproate, and can be best achieved by escalating the dose of lamotrigine

according to clinical response and not to the recommended upper 'therapeutic' doses⁷⁰. The drug has been used in children with myoclonic absences with good results³⁷. Anecdotal evidence suggests that a favourable response on substantial dose of sodium valproate combined with a low to moderate dose of lamotrigine may be lost if lamotrigine is further increased and substitution of sodium valproate is attempted. This combination may augment the risk for allergic skin reaction, and may rarely provoke other adverse immune responses⁷¹.

Ethosuximide. The addition of sodium valproate to ethosuximide may double serum concentration of the latter with concomitant toxicity⁷². Conversely, the addition of ethosuximide may reduce serum level concentration of sodium valproate. Bearing this interaction in mind, the combination of sodium valproate and ethosuximide may be helpful in managing refractory absences⁶⁵, and is probably the first-line treatment of myoclonic absences³⁶.

Clonazepam is considered the most effective anti-absence benzodiazepine and the most powerful drug against myoclonic jerks, with a good effect on GTCS^{73,74}. It may also be effective in photosensitive epilepsy⁷⁵. However, because of its potential to cause sedation and the problem of tolerance⁷⁶, it is usually prescribed as a second-line adjunctive therapy (Table 3). Other adverse effects include fatigue and disturbance of coordination and, less commonly, agitation, confusion and aggressiveness. It is also useful to remember that its combination with sodium valproate during pregnancy may amplify the risk for teratogenicity⁶⁰. Rapid discontinuation should be avoided.

Acetazolamide has a clear anti-absence effect⁷⁷, and may also be useful in JME⁷⁸. Tolerance frequently develops but a period of withdrawal may restore its efficacy. Renal calculi are consequent to its carbonic anhydrase activity and together with rare but severe serious idiosyncratic reactions associated with sulfonamides (rash, aplastic anaemia, Stevens-Johnson syndrome) limit its use as an adjunctive treatment.

Levetiracetam can be effective as monotherapy in JME and other IGE sub-syndromes, and can suppress photosensitivity in combination or monotherapy^{79,80}.

Contraindicated AEDs

Antiepileptic drugs (AEDs) may aggravate pre-existing seizures or induce new seizure types, and such an effect may be either idiosyncratic or syndrome/seizure-related. Factors that hamper the identification of such AEDs include incorrect syndromic and seizure diagnosis, the natural fluctuation of seizure frequency and severity, and the fact that most drug trials are not based on a syndrome and age-specific approach, nor are they designed to detect seizure worsening. Inevitably, most of the existing information on seizure aggravation relies on clinical observations on small series and case studies, and for some drugs such evidence is more convincing than for others. Knowing the drugs that can aggravate idiopathic generalised epilepsies with absences is particularly important as the vast majority have a favourable prognosis.

*Carbamazepine*⁸¹, *vigabatrin*⁸², *tiagabine*⁸³ and *gabapentin*⁸⁴ are contra-indicated in the treatment of TA irrespective of cause and severity. However, carbamazepine may be helpful in controlling GTCS⁸⁴. As GABAergic substances, vigabatrin, tiagabine and gabapentin are associated with induction of absence seizures and absence status epilepticus^{82,85}. The role of *phenytoin* is less clear, and perhaps less aggravating; therapeutic concentrations of phenytoin (and carbamazepine) exacerbate idiopathic generalised epilepsies, particularly those associated with TA, and may induce valproate and benzodiazepine-resistant absence status⁸⁶. These observations are echoed by a well-documented case report of six-week absence status that improved upon discontinuation of phenytoin⁸⁷. On the other hand, it is a common experience (shared also by us) that seizure relapse may occur in patients with well-controlled idiopathic generalised epilepsy on chronic treatment

with phenytoin (as part of a combination, usually with sodium valproate), when discontinuation or substitution of this drug is attempted.

A final note is reserved for the apparently unusual, although probably under-diagnosed, coexistence of IGE and symptomatic focal (temporal lobe) epilepsy, where considerations determining choice of medical therapy may be contradictory⁶. Determination of the most troublesome seizure type (usually these are the partial seizures with or without secondary generalisation) is clearly the primary diagnostic aim and is based on clinical and inter-ictal/ictal EEG criteria (Table 1). Drugs that may have adverse effects on 'primary' generalised seizures such as carbamazepine, vigabatrin and tiagabine should be used with caution and under close monitoring only if absolutely necessary, while those with a broad spectrum of antiepileptic effects such as sodium valproate or lamotrigine are more appropriate⁶.

Conclusion

Optimal management of absence epilepsies, including selection of the appropriate anti-absence drug (and avoidance of the contraindicated ones), advice on lifestyle restrictions, long-term planning of treatment, and definition of the likely outcome, relies on the diagnosis not only of absence seizures but also of possible co-existent myoclonic seizures, or GTCS, or both. As both response to treatment and long-term prognosis are largely syndrome-related, it is clinically important to make as precise a syndromic diagnosis as possible, or *at least attempt to form an initial working hypothesis*. This is because the diagnosis may not be apparent at first presentation, and close clinical and electroencephalographic follow-up may be necessary to complete the final diagnostic jigsaw. For example, a child with newly diagnosed TA does not necessarily have CAE; other generalised seizures (myoclonic jerks or GTCS or both) may subsequently appear, and suggest alternative diagnoses such as JAE or JME, forecasting a different outcome. It is also important to remember that not all generalised epilepsies with absences can fit into the syndromes of IGE recognised by the ILAE. Treatment-wise however, one can still work successfully along the lines of the tree diagram (Table 3), taking into account the type of the associated clinical seizures and their relative preponderance in terms of frequency and severity.

Recognition of possible triggering factors is also essential for appropriate management. Photosensitivity is the most important precipitant of seizures in IGE, and its presence in a child with both spontaneous and photically induced absences would dictate the use of sodium valproate as first choice and at full therapeutic doses, with clonazepam as a second-line drug. On the other hand, if only photically-induced absences and other generalised seizures occur, simple avoidance of stimulus may be sufficient, although in some patients the addition of a small protective dose of sodium valproate may be necessary.

The therapeutic response should be monitored with successive EEG studies. In children the evidence from school is also essential. As in other epilepsies, good compliance must be consistently monitored.

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CHAPTER 12

Adult onset epilepsies**FERGUS J. RUGG-GUNN**

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Not all seizures occurring during adult life are due to epilepsy. Many are acute symptomatic seizures which must be recognised to avoid inappropriate antiepileptic drug (AED) treatment. Acute symptomatic seizures can complicate any acute encephalopathy caused by drugs (particularly alcohol, cocaine, antidepressant overdose) or metabolic disturbance (uraemia, hepatic encephalopathy, etc). They are almost exclusively generalised tonic-clonic seizures that may sometimes be preceded by myoclonus. As seizures of this type rarely present for the first time over the age of 30 years as part of an epilepsy syndrome, one should always have a high index of suspicion about such seizures. Also, acute symptomatic seizures can occur in association with acute cerebral insults such as head injury, stroke, and encephalitis; while their occurrence increases the risk of post-traumatic epilepsy the two are not inevitably linked (see below).

Seizure types in adult epilepsies

Epilepsy may develop in adults for a number of reasons. In the early part of adult life it is common to see a number of patients presenting with idiopathic generalised epilepsies, particularly juvenile myoclonic epilepsy and epilepsy with waking tonic-clonic seizures. Such epilepsies will be characterised by a high probability of generalised spike and wave in the EEG, and patients will be neurologically normal and not require further investigation.

Most other patients presenting with epilepsy in adult life will have a form of focal epilepsy. This may be overtly declared by the presence of an aura to seizures that clearly identifies the localised onset. However, patients will be seen in whom the focal onset does not result in significant symptoms that can be recalled subsequently by the patient, or witnessed by observers. This is particularly the case for seizures that occur during sleep. All seizures occurring during sleep which commence during adult life must be regarded as being of focal onset unless proven otherwise.

While the onset of a partial epilepsy during adult life is more commonly associated with the identification of an underlying neurological disorder than is the case with epilepsies developing in childhood, it must be recognised that over 50% of patients with adult onset epilepsy have no aetiology that can be determined by the investigative means currently available, although this proportion is decreasing as advances in magnetic resonance imaging occur. A number of aetiological groups of adult onset epilepsies will be considered here in more detail.

Causes of adult-onset epilepsy*Post-traumatic epilepsy*

The incidence of post-traumatic epilepsy varies depending on the population studied. The best available information on the risk of epilepsy following head injury comes from the community-based survey summarised in Table 1. This would indicate that mild injuries (e.g. injuries not

complicated by skull fracture and with a post-traumatic amnesia of less than 30 minutes) do not carry a significantly increased risk of the development of epilepsy, but that more severe injuries probably do. However, a more recent population-based study from Denmark suggests that even mild head injuries (loss of consciousness for less than 30 minutes, post-traumatic amnesia for less than 24 hours, confusion/disorientation, or focal, transient neurological deficit) may be associated with an increased risk¹. Different definitions of a 'mild' head injury are the most likely explanation for the discrepancy between these studies.

A number of factors influence the risk of epilepsy:

Missile injuries. Several series have looked at the incidence of epilepsy following missile injuries to the head. The best estimate of the risk of epilepsy for such injuries overall would seem to be 50%. A number of factors further influence this risk, and these are summarised in Table 2.

Non-penetrating head injuries. This form of head injury has been widely studied but largely in patients admitted to neurosurgical units. It must be remembered that these represent a selected population of head-injured patients.

If seizures are going to complicate a head injury they tend to do so shortly after injury. Around 75% of patients will have their first post-traumatic seizure within a year of injury, whether this is a missile or blunt injury. Whilst the risk of developing seizures decreases with the passage of time there are no good grounds for differentiating between seizures that occur in the first week and later seizures, as far as their significance is concerned. One exception is that seizures occurring immediately after impact do not carry an adverse prognosis for recurrent seizures.

Jennett defined early seizures as those occurring within seven days of injury². A total of 25% of patients with early seizures had late epilepsy, compared to 3% of patients developing late epilepsy in the absence of early seizures. When other factors contributing to the risk of late post-traumatic epilepsy were excluded, i.e. depressed fracture or haematoma, late epilepsy occurred in only 1.2% in the absence of early seizures, but in 51% of patients in whom early seizures occurred.

The other factors which clearly contribute to the risk of late epilepsy are the presence of an acute intracranial haematoma (31% risk) and depressed skull fracture (15% risk). In patients without these features longer periods of post-traumatic amnesia increase the risk of epilepsy.

The risk of epilepsy shortly after traumatic brain injury is high, but how long this high risk lasts is unknown. In a large population-based study in Denmark, it was found that the risk of epilepsy was increased after a mild brain injury (RR 2.22, 95% CI 2.07-2.38), severe brain injury (7.40, 6.16-8.89), and skull fracture (2.17, 1.73-2.71). The risk continued to be increased more than 10 years later in each group. Interestingly, patients with a family history of epilepsy had a notably high risk of epilepsy after mild (5.75, 4.56-7.27) and severe brain injury (10.09, 4.20-24.26). It appears therefore that even mild head injuries, particularly in susceptible individuals, are associated with a greater long-term risk of developing epilepsy compared to the general population¹.

There seems no doubt that the prognosis for post-traumatic epilepsy is considerably worse than for epilepsy for which no cause is found. Caveness reported a remission rate of approximately 50%³. Jennett's series reported a remission rate of 25%, but one-third of patients continued to have frequent seizures. There is some evidence that the later the onset of epilepsy following head injury the less likely is remission. Furthermore, seizures appearing to arise from the temporal lobes seem to have a worse prognosis than those arising elsewhere.

Table 1. Head injury.

	Number of patients	Risk of epilepsy		Relative risk vs expected risk
		1 year (%)	5 years (%)	
Severe injuries (brain contusion, intra-cranial haematoma or PTA > 24 hours)	195	7.1	11.5	29
Moderate injuries (skull fracture or PTA >30 mins)	92	0.7	1.6	4.0
Mild injuries (no fractures PTA <30 mins)	1640	0.1	0.6	1.5 (95% CI 0.6-3.3)
Expected rates			0.4	

PTA = post-traumatic amnesia

Table 2. Factors influencing risk of epilepsy after missile injuries.

Frontal injury
Persistent hemiparesis
Surgical removal of metal
Complicating infection
- abscess
- fungal infection

There is little evidence to suggest that early AED therapy has a significant effect in preventing the development of later epilepsy. This may either be because AEDs do not influence the natural history of this form of epilepsy, or because head-injured patients show a marked tendency to be non-compliant with prophylactic therapy.

Post-operative epilepsy

The overall incidence of post-operative seizures in a five-year period following supratentorial craniotomy is approximately 17%. The incidence may vary from as low as 3% to as high as 92% depending on the condition for which craniotomy is carried out.

A total of 20% of patients undergoing surgery for intracranial aneurysms will develop post-operative seizures. The risks are low for aneurysms of the internal carotid (7.5%) but high for aneurysms of the anterior communicating (21%) and middle cerebral artery (38%). Surgery for arteriovenous malformations (AVMs) and spontaneous intracerebral haematomas carries a 50% and 20% risk of *de novo* epilepsy, respectively. A considerable portion of this risk seems to be directly attributable to surgery, as the risk of epilepsy associated with aneurysms managed conservatively was approximately 8% in 261 patients and an approximately 20% risk over 20 years for AVMs managed conservatively.

The incidence of epilepsy following surgery for supratentorial abscess is extremely high, and virtually all patients develop seizures if followed up for a sufficiently long period of time. The risk of seizures complicating insertion of an indwelling ventricular shunt is about 24%.

The risk of tumour surgery causing epilepsy is more difficult to identify, particularly for progressive tumours such as gliomas. Seizures may develop *de novo* following surgery for meningioma in 22% of cases, though approximately 40% of meningioma patients who had pre-operative seizures do not have further seizures post-operatively. Once again there is a clear relationship between time of surgery and the development of seizures. Approximately 70% who have seizures will have done so by one year and 90% by two years post-operatively. To date there is no evidence that early prophylactic treatment with AEDs significantly reduces the risk of post-operative seizures.

Tumour epilepsies

Tumours remain a relatively rare cause of epilepsy but the incidence of tumour epilepsy is clearly age related. In one series tumours were detected in 16% of patients developing epilepsy over the age of 20, and in 22% of patients developing partial epilepsy over this age. The diagnosis of tumour-based epilepsies is usually straightforward and indicated by the presence of developing focal neurological signs and symptoms, a focal EEG abnormality and by neuroimaging. In patients with benign tumours who present only with epilepsy diagnosis is difficult and management even more problematic.

There is no doubt that the more benign the tumour the more likely it is to present with a history of epilepsy (Table 3). The siting of the tumour also appears to influence the likelihood of a presentation of epilepsy (Table 4). The likelihood of finding a neoplastic basis for epilepsy beginning in adult life is influenced by partial seizure type (Table 5).

Cerebrovascular epilepsy

Cerebrovascular disease is an important contributor to new cases of epilepsy developing over the age of 60 and is largely responsible for the increased age-related incidence at this time of life. Overall, a number of studies would suggest that between 5 and 10% of patients with a clinical history of stroke due to occlusive vascular disease will develop epilepsy. However, covert cerebrovascular disease may be much more common on the CT scans of patients with late-onset epilepsy when compared with age-matched controls⁵. The Oxford Community Stroke Study found that 2.8% of patients had a seizure before their first stroke. A total of 2.1% had a seizure within 24 hours of the stroke and 7.1% had seizures subsequently.

Table 3. Incidence of seizures due to different tumours.

Tumour types	Percentage presenting with seizures
Astrocytoma	70
Oligodendroglioma	92
Malignant glioma	37
Meningioma	67
Metastasis	47
Pituitary adenoma	9

Table 4. Incidence of seizures due to tumours at different sites.

Site	Percentage with fits
Frontal	53
Parietal	68
Temporal	48
Occipital	32
Third ventricle	32
Thalamic	8
Pituitary region	8

Table 5. Types of partial seizures and tumour aetiology.

	Number of patients with partial seizures	Percentage identified as having tumour
Simple motor seizures	1211	21
Somatosensory seizures	98	56
Other simple sensory seizures	148	24
Complex partial seizures	228	13

After MAUGUIERRE and COURJON, 1978⁴

A review article by Myint PK *et al*²¹ also quotes the 1997 Oxfordshire community stroke project. This showed that, overall, 11.5% of patients are at risk of developing post-stroke delayed or late onset seizures within five years²². Furthermore, the paper reports data from Naess H *et al*, stating that the risk of a seizure post-stroke in young people is 10.5% at 5.7 years²³. This is most likely due to the presence of larger cortical infarcts in young adults rather than small vessel disease related lacunar events which are less likely to cause cortical irritability.

A more recent study has however suggested a lower incidence of post-stroke epilepsy, as defined by 2 or more seizures, in young adults (<65 years of age) at 10.7% at 10 years²⁴. Furthermore, this included data from all patients irrespective of severity of the initial stroke, and this is relevant when considering the subsequent risk of developing seizures. Similar, recent studies have also reported lower rates of post-stroke epilepsy. For example, Serafini *et al*, showed a rate of 1.97% at 2 years (0.985% averaged annual risk) for ischaemic stroke²⁵. Bryndziar *et al*. reported a rate of 4.4% at 6.5 years (0.67% averaged annual risk)²⁶.

Actuarial analysis estimated that the one-year cumulative risk of a post-stroke seizure was 4.1% after cerebral infarction, 18.2% after primary intracerebral haemorrhage and 27.8% after subarachnoid haemorrhage. Stratification of risk is therefore important to more accurately ascertain the risk to an individual. A number of risk factors for the development of post-stroke seizures have been established from a several published studies^{24,27}. In ischaemic stroke, the severity of the initial neurological deficit, the Glasgow Coma Score, stroke severity indices, the severity of the persistent disability after the stroke, the involvement of multiple sites, cortical damage and hippocampal involvement are prognostic determinants. In a multivariate analysis of data from a large population-based study of post-stroke epilepsy, a higher risk was associated with age <65 years, a total anterior circulation infarct, dysphasia, visual neglect, incontinence and dysarthria²⁴.

Most recently, it has become possible to quantitatively determine the risk of developing post-stroke epilepsy in an individual patient using a validated scoring system²⁸ (Galovic M *et al*. 2018). In general, for an unstratified cohort, this showed a risk of seizures post-stroke at 4% in the first 12 months and then 1% per year up to 5 years post-stroke. The use of the scoring system permitted stratification of patients with the lowest scores being associated with a 1.3% risk of stroke over 5 years and the highest scores predicted a 83% risk over 5 years.

The higher risk during the initial 12 months is consistent with previous reports showing that late-onset seizures (>2 weeks after the stroke) have a peak incidence within 6–12 months after the stroke²⁹.

Epilepsy also complicates cerebral aneurysms whether or not they have bled or been operated upon (see above). AVMs are also a cause of epilepsy in earlier life. Epilepsy is present in approximately 20–25% of patients presenting with AVMs and the risk of developing *de novo* epilepsy in AVM is approximately 1% per annum. Haemorrhage and surgical treatment appear to be the major factors that increase this risk.

Autoimmune epilepsy

Seizures are a common presenting symptom in autoimmune neurologic disorders, particularly in limbic encephalitis or multifocal paraneoplastic disorders⁶⁻⁹. Autoantibodies recognised with paraneoplastic limbic encephalitis include antineuronal nuclear antibody type 1, collapsin response-mediator protein 5 (CRMP-5), and Ma2. Voltage-gated potassium channel (VGKC) complex and glutamic acid de-carboxylase 65 (GAD65) antibodies, often nonparaneoplastic in aetiology, have been reported in patients with limbic encephalitis and idiopathic epilepsy with AED-resistant seizures^{10,11}. Newly identified autoantibody specificities that strongly correlate with clinical seizures include N-methyl-D-aspartate (NMDA), γ -aminobutyric acid B^{12,13} and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors¹⁴.

It is clear that the clinical spectrum of auto-immune epilepsy is still unknown. In a series of patients with epilepsy, VGKC complex antibodies were detected in 10%; NMDA receptor antibodies, in 7% of newly diagnosed patients; and GAD65 antibodies, in 1.6–1.7%¹⁵. It is conceivable that only patients with the most severe presentations in this heterogeneous group are being identified.

Accumulating data support an autoimmune basis in patients with AED-resistant seizures, including those lacking a typical 'limbic encephalitis' phenotype. Identification of an immune basis is important because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process in these patients. In a cohort study, autoimmune antibodies were detected in 14% of patients with epilepsy¹⁶. This study, along with several case reports and series, suggested a potential benefit of immunotherapy in improving seizure control.

Recurrent seizures are the early and predominant clinical manifestation in patients with an autoimmune aetiology. An autoimmune cause is identified most readily in patients who present with the full syndrome of limbic encephalitis, characterised by subacute memory impairment with mood disturbance and temporal lobe seizures (see Table 6). LGI-1-antibodies are often associated with frequent, multi-focal seizures, including faciobrachial dystonic seizures, thermal or shivering sensory seizures, piloerection, cardiac arrhythmias and subclinical seizure activity³⁰. The diagnosis of autoimmune limbic encephalitis is aided by detection of neural autoantibodies with radiological or pathological evidence of mesial temporal lobe inflammation and in some cases a history of neoplasia in the preceding five years¹⁷.

In addition to the presence of neural antibodies, clinical features suggestive of autoimmune epilepsy include:

- Acute to subacute onset, with seizures occurring every three months or less
- Multiple types of seizures or faciobrachial dystonic seizures
- Resistance to anti-seizure medication
- Personal or family history of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation.

When autoimmune epilepsy is suspected on clinical grounds, CSF evaluation and comprehensive screening for neural autoantibodies are indicated. If autoimmune epilepsy is suspected, a trial of immunotherapy – intravenous steroids or intravenous immunoglobulin, (IVIg) – is justifiable in the absence of other treatment options and may serve as additional evidence for an autoimmune aetiology when a favourable seizure response is observed^{18,19}.

Models based on a number of these features have recently been validated and may be useful in establishing a diagnosis and predicting the response to immunotherapy³¹.

Questions remaining unanswered include the natural history of autoimmune epilepsy, the selection criteria for patients with epilepsy most likely to benefit from an autoimmune evaluation, the timing for immunotherapy trial, and optimal duration of long-term immunotherapy maintenance³².

Epilepsy after cerebral infection

The risk of epilepsy after viral encephalitis has been estimated to be 10–25%, and 3–10% after bacterial meningitis, particularly if a fixed neurological deficit has been acquired²⁰. Uncomplicated viral meningitis has not been associated with an increased risk of seizures.

Table 6: Clinoradiological characteristics of VGKC-complex, NMDA, GAD and AMPA antibody associated encephalitis. (from BAKPA OD *et al*³²)

Characteristic features	LG11>CASPR2 (VGKC-complex)	NMDAR	GAD	GABABR	AMPA
Gender	M>F	F>M	F>M	M>F	F>M
Typical age group	>50 years	<40 years	>20 years	> 40 years	> 40 years
Neurological features	Memory loss Confusion Temporal lobe seizures FBDS	Multistage encephalopathy with: Psychiatric symptoms Extratemporal seizures Movement disorders Autonomic instability Coma	Memory loss Temporal lobe seizures Coexisting autoimmune disorders including T1DM, SPS	Memory loss Seizures Confusion	Amnesia Seizures Insomnia Confusion
Psychiatric Features	Psychosis Personality changes Depression Anxiety	Psychosis Behavioural disturbances Delusions Agitation	Depression Anxiety	Psychosis Hallucination Behavioural changes	Psychosis Confabulation Agitation Personality changes
Characteristic seizures	FBDS CPS GTC	GTC SE CPS	GTC CPS	CPS GTC SE Focal motor	GTC CPS
Tumour association	Thymoma SCLC	Ovarian teratoma	SCLC	SCLC	Thymoma SCLC
Target antigen	LG11 & CASPR2	NR1 subunit	GAD-65	GABA _B R	GluR1/2
MRI	High signal change in MTL, less commonly basal ganglia	Normal although non-specific signal changes in medial temporal structures	Normal, although increased signal in MTL	Increased signal in MTL	Increased signal in MTL
EEG	Focal or generalised slowing	Extreme delta brush, focal or diffuse delta/theta activity	Focal or generalised slowing	Focal or generalised epileptic activity	Focal epileptic activity
Treatment & outcome	Good response to immunotherapy	Responds slowly to immunotherapy	Poor treatment outcome with immunotherapy and AEDs	Good response to immunotherapy	Relapses are common although there is good response to immunotherapy

AED = Antiepileptic drugs; AMPAR = Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CSF = Cerebrospinal fluid; CASPR2 = Contactin-associated protein2; CV2/CRAMP5 = Collapsin response mediator protein; CPS = Complex partial seizure; EEG = Electroencephalogram; FBDS = Faciobrachial dystonic seizures; GTC = Generalized tonic clonic; GABA = Gamma aminobutyric acid; GlyR = Glycine receptor; GluR = Glutamate receptor; GAD = Glutamic acid decarboxylase; LGI1 = Leucine-rich glioma inactivated1; MRI = Magnetic resonance imaging; MTL = Medial temporal lobe; NMDAR = N-methyl-d-aspartate; OCB = Oligoclonal bands; SE = Status epilepticus; SOX1 = Sex determining region Y-box 1; SPS = Stiff Person Syndrome; SCLC = Small cell lung cancer; T1DM = Type 1 diabetes; VGCC = Voltage gated calcium channel.

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CHAPTER 13

Temporal lobe epilepsy**BEATE DIEHL AND JOHN S. DUNCAN**

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In community studies, the cumulative incidence of non-febrile seizures is about 20 per 1000. The prevalence of active epilepsy is 5 per 1000 and about 50% of these patients have seizures (16 patients with active focal epilepsy in a population of 6000). About 60–70% of focal seizures originate in the temporal lobe. It has been attempted to link seizure semiology to activation of different anatomical regions of the temporal lobe. One attempt was to divide temporal lobe seizures into opercular, temporal polar, and basal or limbic types¹; whether such detailed classification schemes are valid or useful is debatable. The distinction into mesio-basal and lateral neocortical types however is widely accepted, and even though symptomatology overlaps and spread from lateral to mesial cortex (and vice versa) is common, this remains a useful distinction².

Epilepsy arising in the medial temporal lobe (MTLE) (see Table 1)

The commonest pathology underlying this type of epilepsy is hippocampal sclerosis^{3,4}, and the entity of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) is recognised as a distinctive constellation among the focal epilepsies⁵. This pathology is associated with febrile convulsions in young children (particularly complex prolonged febrile convulsions), possibly due to a factor predisposing the child to febrile seizures or maybe as the result of a complex febrile convulsion. Other pathologies include dysembryoplastic neuroepithelioma and other benign tumours, cavernous angiomas, glioma, malformations of cortical development, or gliosis as a result of encephalitis or meningitis.

The symptoms during epileptic seizures may be subjective only (epileptic auras, with clear consciousness) or may progress to seizure signs that can be observed and analysed when recorded during video EEG recordings, often associated with impairment of awareness⁶.

For the updated ILAE seizure classification and a practical guide see^{18,19}.

Seizures arising from the temporal lobe typically have a relatively gradual evolution (compared to extra-temporal seizures), develop over 1–2 minutes, have an indistinct onset with partial awareness at the onset and last longer than most extra-temporal seizures (2–10 minutes). Often, three components can be seen:

1) *Aura*. An aura is defined as a subjective feeling typically involving sensory or psychic phenomena only. It may comprise visceral, cephalic, gustatory, olfactory, déjà vu or affective symptoms and fear. The rising epigastric sensation is the commonest aura, others include perceptual or autonomic auras. Ictal events arising in the amygdala commonly have several different types of auras. Autonomic symptoms include changes in skin colour, blood pressure, heart rate, pupil size, and piloerection. Speech usually ceases or is severely reduced, but occasionally repetitive vocalisation may occur. Simple auditory phenomena such as humming, buzzing, hissing, and roaring may occur

if the discharges arise in the superior temporal (Heschl's) gyrus; and olfactory sensations, which are usually unpleasant and difficult to define, can signal the start of seizures in the sylvian region or ento-rhinal cortex.

In the new operational ILAE classification of seizures, auras correspond to focal aware seizures.

Table 1. Features of focal seizures of medial temporal lobe origin.

Clinical Features

- Past history of prolonged febrile convulsions (in those with medial temporal sclerosis)
- Seizures longer than frontal lobe seizures (typically > 2 min), with a slower evolution and more gradual onset/offset
- Auras common. Typical of medial temporal (rather than lateral temporal origin) are visceral, cephalic, gustatory, affective, perceptual or autonomic auras
- Partial awareness commonly preserved, especially in early stages, and slow evolution of seizure
- Prominent motor arrest with loss of awareness (the 'motionless stare')
- Post-ictal confusion and dysphasia common
- Autonomic changes (e.g. pallor, redness, and tachycardia)
- Automatisms. Often less violent than in frontal lobe epilepsy, and usually oro-alimentary (lip-smacking, chewing, swallowing), or gestural (e.g. fumbling, fidgeting, repetitive motor actions, undressing, walking, running) and sometimes prolonged. Vocalisation also common. Other motor automatisms can occur.

EEG

Inter-ictal:

- Epileptiform abnormalities: Anterior or mid-temporal spikes/sharp waves (best shown on sphenoidal electrodes)
- Non-epileptiform abnormalities: regional slowing in temporal lobe regions (EEG signs can be unilateral or bilateral)

Ictal:

- Rhythmic temporal theta activity within 30 seconds of onset (in ~80% of MTLE seizures)

Imaging

- Hippocampal sclerosis (demonstrable by unilateral decrease in hippocampal volume and increase in signal on T2-weighted MRI scan)
- Structural lesion (most commonly: hamartoma, other benign tumours, glioma, cavernous angioma, malformation of cortical development)

This table includes those clinical features particularly characteristic of temporal lobe epilepsy. In many cases, however, these features do not occur. However, these features do not occur.

More complex hallucinatory or illusionary states are produced with seizure discharges in association areas (e.g. structured visual hallucinations, complex visual patterns, musical sounds, and speech). A cephalic aura can occur in temporal lobe seizures, but also occurs with a frontal lobe focus.

2) *Blank spell.* Motor arrest with altered awareness (the so-called 'motionless stare' or 'dialeptic' in the semiological seizure classification⁷ or in the past also called 'dyscognitive'⁸ seizure; now focal impaired awareness seizure) is prominent, especially in the early stages of seizures arising in medial temporal structures, and more so than in extratemporal lobe epilepsy.

3) *Automatism.* The automatisms of mediobasal temporal lobe epilepsy are typically less violent than in frontal lobe seizures, and are usually oro-alimentary (lip-smacking, chewing, swallowing), or gestural (e.g. fumbling, fidgeting, repetitive motor actions, undressing, walking, running), and sometimes prolonged. Manual automatisms may occur only or predominantly on one side; this is ipsilateral to the side of ictal onset, particularly if contralateral dystonic posturing is present. Vocalisation is also common, and other motor automatisms can occur. If speech with identifiable words occurs during a seizure (ictal speech) this suggests a non-dominant seizure focus (see Loddenkemper and Kotagal⁹ for a review of lateralising signs).

Post-ictal confusion and headache are common after focal seizures with loss of awareness arising from the temporal lobe, and if dysphasia occurs this is a useful lateralising sign indicating seizure origin in the speech-dominant temporal lobe¹⁰. Post-ictal nose-rubbing is commonly seen in temporal lobe epilepsy, and in 90% of cases is ipsilateral to the focus¹¹. Amnesia is the rule for the blank spell and the automatism. Secondary generalisation is much less common than in extra-temporal lobe epilepsy. Patients often complain of poor memory for recent events, and this may get worse as the epilepsy continues.

The inter-ictal EEG in mediobasal temporal lobe epilepsy usually shows anterior or mid-temporal spikes. Sphenoidal electrodes may occasionally be necessary for their detection. Other changes include intermittent or persisting slow activity over the temporal lobes. The EEG signs can be unilateral or bilateral. Modern MRI will frequently reveal the abnormality underlying the epilepsy (see Chapter 21).

Epilepsy arising in the lateral temporal neocortex (see table 2)

There is considerable overlap between the clinical and EEG features of mediobasal and lateral temporal lobe epilepsy^{12,13}. There is often a detectable underlying structural pathology, the commonest being a glioma, cavernous angioma, hamartoma, dysembryoplastic neuroepithelial tumour, other benign tumour, malformation of cortical development, and damage following trauma. There is no association with a history of febrile convulsions. Consciousness may be preserved for longer than in a typical medial temporal seizure.

The typical aura includes hallucinations which are often structured and of visual, auditory, gustatory, or olfactory forms (which can be crude or elaborate) or illusions of size (macropsia, micropsia), shape, distance, or sound. Affective, visceral or psychic auras occur but are less common than in mediobasal temporal lobe epilepsy. The automatisms can be unilateral and have more prominent motor manifestations than in mediobasal temporal lobe epilepsy. Post-ictal phenomena, amnesia for the attack and psychiatric comorbidity are as common in this form of temporal lobe epilepsy as in the mediobasal form.

The inter-ictal EEG often shows spikes over the temporal region, maximal over the lateral convexity rather than inferomedial electrodes. Hippocampal volumes and T2 measures on MRI scanning are usually normal, in contrast to medial temporal epilepsy, and MRI will reliably demonstrate the other

structural lesions responsible for the epilepsy (although in some patients, imaging studies are normal) (see Chapter 21). Cortical stimulation may elicit the symptoms of seizures¹⁵.

Pharmacological options for temporal lobe epilepsy are the same as for other focal epilepsies, and surgical treatment may be an option if medication is unsuccessful¹⁴ (Section Nine). Class 1 evidence comparing continued medical treatment against temporal lobectomy supports that surgery is superior to prolonged medical therapy¹⁶. Even if scalp EEG suggests bitemporal lobe epilepsy, intracranial EEG recordings may reveal unilateral seizure onset, and, particularly in the context of unilateral hippocampal sclerosis or non-lesional temporal lobe epilepsy, surgical outcomes can still be favourable¹⁷.

Table 2. Features of focal seizures of lateral temporal lobe origin.

Clinical features

- Typically no history of febrile seizure
- Auras common. Hallucinations (especially auditory) or illusions more suggestive of lateral rather than mesial temporal origin, but any other temporal lobe aura may occur
- The motionless stare and the automatisms are similar to those in medial temporal lobe epilepsy

EEG

- Spikes and focal discharges from the temporal region

Spikes may have a lateral (posterior) temporal maximum, rather than an anterior temporal/sphenoidal maximum. Polyspikes are more commonly seen with neocortical generators

Imaging

- Structural changes (especially malformation of cortical development, benign tumour, glioma, post traumatic changes, cavernous angioma)

This table includes those clinical features particularly characteristic of temporal lobe epilepsy. In many cases, however, these features do not occur.

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CHAPTER 14

Frontal lobe epilepsy

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While frontal lobe epilepsy accounts for only 10-20% of patients in surgical series, the prevalence in non-surgical cohorts is probably higher. Frontal lobe epilepsy (FLE) represents 20-30% of focal epilepsies; calculating the prevalence of FLE in the UK from the National Institutes of Health estimates for the USA gives a figure of about 115,000, of whom 35,000 remain refractory to medical treatment. In 2017, the International League Against Epilepsy has proposed an updated classification of seizure types (1981; updated 2017 classification systems¹). Different clinical manifestations can be compartmentalised into anatomical subdivisions of the frontal lobes of which there are many, with diverse functions (see below). However, FLE presents some particular diagnostic problems, both in the clinical and the electrographic diagnosis of seizure types. The extensive anatomical connections between subdivisions of the frontal lobe and between the frontal and other lobes blur these categories. Seizures may, for example, spread from temporal to orbitofrontal cortex (or vice versa) within milliseconds, giving substantial overlap between the seizure manifestations documented from these two regions². FLE in general has been less well studied than temporal lobe epilepsy. Some consider that seizure freedom after surgery is the most reliable way of defining a particular localised syndrome and thus various conceptual aspects of FLE remain poorly understood.

Aetiology

In a large series of 250 cases operated on for FLE³:

Head injury	77
Tumour	63
Birth trauma	26
Gliosis (from abscess, haematoma etc)	14
Encephalitis	13
Gunshot	11
Other known	17
Unknown	29

The spectrum is likely to be different for those cases not requiring surgery, e.g. fewer tumours, but post-traumatic epilepsy is commonly frontal. Series with modern neuroimaging data show that tumours, malformations and vascular anomalies are also not infrequently detected. The cause in many cases remains unknown.

Clinical diagnosis

The evolution in time of frontal lobe seizures. The seizures which most of the time occur without warning, are often short and are followed by very rapid recovery. They frequently occur from sleep,

and may occur in clusters of 5–6 or more per night, usually with partial recovery between, but status epilepticus is also common.

Seizure manifestations^{2,4-7,9}. The seizure semiology is dependent on the area of cortex activated during a seizure and, therefore, can give important clues as to the presumed epileptogenic zone. However, the area of cortex generating symptoms during seizures need not be identical with the epileptogenic zone, as spread frequently occurs from the area of ictal onset. Understanding the functional anatomy of the frontal lobes allows us to link clinical symptoms during the seizure and areas of cortex activated, and electro-clinical characteristics have been recently summarised¹⁹⁻²¹. For practical purposes in epileptology the main areas of the frontal lobe are defined by stimulation and lesion studies and include:

The primary motor areas (precentral gyrus); supplementary sensorimotor areas (SSMA) in the mesial aspect, the posterior part of the superior frontal gyrus and in the paracentral lobule; the frontal eye field in the posterior part of the middle frontal gyrus; the frontal language area in the pars opercularis and triangularis in the dominant inferior frontal gyrus; the prefrontal cortex; and the orbitofrontal cortex. Negative motor areas are represented in the posterior inferior frontal gyrus and in the posterior mesial superior frontal gyrus in front of the SSMA proper.

Frontal lobe seizure semiology with predominantly positive motor symptoms (focal aware or unaware motor onset seizures) can be grouped into three main categories: 1) focal clonic seizures; 2) bilateral asymmetrical tonic seizures; 3) complex motor seizures; 4) other rarer seizure semiologies as listed below.

1. Classical, hemiclonic Jacksonian motor seizures are the easiest to localise, invariably involving the contralateral motor strip. Consciousness is usually preserved. There may be a short preceding aura (non-specific or sometimes somatosensory, the latter likely in part due to some overlap of motor and sensory representations in the pericentral region).
2. More anteriorly, in the supplementary motor area (SMA) medially and the premotor cortex (PMC) laterally, more complex motor manifestations are recognised: turning of head and eyes and posturing of arms and legs. Classically, SMA seizures cause sudden assumption of a 'fencing posture', the contralateral arm being abducted at the shoulder, externally rotated, flexed at the elbow. Though characteristic, these seizures are not pathognomonic of SMA, or even frontal, onset. Motor automatisms may occur, particularly in PMC seizures, although it is not entirely clear whether this is partly due to temporal lobe involvement. The seizure may be preceded by a vague somatosensory aura such as numbness or tingling, more poorly localised than in parietal seizures. Vocalisation at the onset of the seizure is also common. These motor manifestations may be ipsilateral, contralateral or bilateral from a unilateral discharge. Consciousness may be retained. Secondary generalisation may be too rapid for the posturing to be detected.
3. Complex motor seizures. Such seizures may arise from frontopolar, anterior cingulate, opercular-insular and orbitofrontal regions. There is usually complex motor activity, usually considered 'hypermotor', 'gestural' or 'repetitive'. There may be somatic, experiential or psychic aura, and so these may cause confusion with temporal lobe seizures; there may be an aura including epigastric sensations and olfactory hallucination. Autonomic manifestations are common, e.g. facial flushing and/or pallor, tachycardia, pupillary dilatation and incontinence of urine. Speech arrest may be seen, particularly in dominant hemisphere seizures, and there may be a post-ictal phase of predominantly expressive dysphasia. Spread of the seizure discharge posteriorly may produce PMC and SMA manifestations. Motor automatisms are common.

4. Rarer seizure types include: seizures characterised by brief lapses of awareness (focal impaired awareness seizures), which are mainly seen with anterior mesial frontal seizures, frontopolar or orbitofrontal seizures; in addition, akinetic seizures, aphasic seizures or seizures characterised by early head version without loss of awareness.

Spread of seizure discharges may occur very rapidly between the hemispheres, resulting in sudden hypertonia, or less frequently hypotonia, causing drop attacks with severe injury. The seizure may: a) continue in the same phase on the ground, b) progress to a generalised clonic seizure, or c) there may be rapid recovery.

Electroencephalography

Inter-ictal EEG recordings are often challenging and it has been reported that up to 40% of patients with FLE do not have inter-ictal epileptiform discharges. The yield of prolonged video EEG recordings and careful review of EEG samples with closely spaced midline electrodes may be of higher yield. Ictal scalp recording of EEG changes in FLE is hampered by the size of the frontal lobes, which means that signals from distant, mesial or deep gyral discharges may be attenuated and undetectable^{8,9}. Where detected, the spatial resolution and discharge localisation is often very poor. As motor manifestations are prominent, often without any aura, ictal scalp EEG recording is often swamped by muscle artifact and thus uninterpretable. Post-ictal EEG suppression may be very short. Localisable ictal EEG changes were found in 30–40% of cases.

Intracranial EEG recordings using subdural grid electrodes and/or depth electrodes may be necessary in lesional cases where exact delineation of extent of epileptogenicity is necessary, in addition to allowing for mapping of eloquent cortex using cortical stimulation. In non-lesional cases invasive EEG can be undertaken if there is a clear hypothesis of the ictal onset zone. However, intracerebral studies suffer from sampling error, only detecting discharges that are very near the electrodes. Without accurate information to guide electrode placement, this too is often unsuccessful.

Imaging

Even in refractory FLE the detection rate of imaging is poorer than in temporal lobe epilepsy (TLE)⁹. Computed tomography identifies abnormalities with localising value in about 20% of cases and magnetic resonance imaging in a further 30–40%. Positron emission tomography frequently shows abnormalities but these are commonly rather non-specific. As magnetic resonance imaging becomes more sensitive, small areas of dysplasia and heterotopia are increasingly detected; their clinical significance remains to be evaluated. The size of the frontal lobes means the location of the lesions responsible for FLE is more variable than for TLE.

Frontal versus non-epileptic seizures

It has been recognised that some seizures previously labelled as non-epileptic are in fact due to FLE. The reasons for the confusion include:

- Motor activity in FLE is frequently bizarre and complex
- Bilateral motor activity may occur in FLE with partial preservation of awareness
- The inter-ictal EEG may be normal, and the ictal changes obscured by artifact.

There are some differentiating features: epileptic seizures are often stereotyped for an individual, shorter and commonly occur from sleep. Caution should be exercised in diagnosing seizures arising purely from sleep as being non-epileptic. An earlier age of onset favours an epileptic basis.

Non-epileptic seizures show more fluctuation in the level of motor activity. Some qualitative differences in the movements have been suggested but these are less clear-cut¹⁰.

Frontal lobe seizures versus parasomnias

Paroxysmal motor disorders occurring from sleep include not only frontal lobe seizures, but also parasomnias. There are benign, unpleasant or undesirable behavioural or experiential phenomena that occur predominantly or exclusively during sleep. To a reasonable degree parasomnias, such as sleep-walking or sleep tremors, can be distinguished from frontal lobe seizures by clinical inquiry. Events in parasomnias tend to last longer individually, are less likely to occur in clusters in a given night, are more likely to cause complex behaviours, such as wandering outside the bedroom, and tend to be less stereotyped than frontal lobe seizures. Prolonged EEG with videopolysomnography may be required to distinguish parasomnias from frontal lobe seizures. A clinical scale has recently been validated and may obviate the need for prolonged monitoring in some cases¹¹.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE is a distinctive disorder, with autosomal dominant (Mendelian) inheritance¹². A number of families have been described across the world. The seizure pattern is remarkably consistent, with predominantly nocturnal clusters of brief motor seizures, which may be complex or even violent. Though the semiology may vary between members of the same kindred, seizures are stereotyped within a given individual. Consciousness may be retained. Neuroimaging is normal, as may be the inter-ictal and even ictal EEG. Videosomnography differentiates the condition from parasomnias. Mutations in the neuronal nicotinic acetylcholine receptor alpha-4 and beta-2 subunits (CHRNA4 and CHRN2) have been identified^{12,13}. However, these genes are not mutated in the majority of kindreds, suggesting genetic heterogeneity despite the clinical homogeneity (see also Chapter 5). Carbamazepine is usually effective treatment.

Treatment

The pharmacological treatment of FLE is as for other focal epilepsies. There are no good comparative drug trials specific to FLE. Surgery is less successful than for TLE with complete remission after focal resection in only 20–40%, even in the most highly selected cases³, though some newer reports document better outcomes¹⁴. Seizure freedom rates decline over the years. A recent large series has analysed 70 patients who underwent a frontal lobectomy between 1995 and 2003. A favourable outcome was defined as complete seizure freedom, allowing for auras and seizures restricted to the first post-operative week. The estimated probability of complete seizure freedom was 55.7% at the first postoperative year, 45.1% at three years after surgery, and 30.1% at five years¹⁵. It should be noted that, in addition to patients becoming seizure free, a significant percentage of patients experience an 80% or more reduction in their seizures. Another recently published cohort of frontal lobe surgeries documented 55% seizure freedom rate at seven years after surgery¹⁶. Completeness of resection of a visible lesion remains one of the most important predictors of good outcome. Surgery need not be associated with increased neurological or neuropsychological deficit.

Corpus callosum section may be of benefit in patients with drop attacks, who are at risk of major injury. This may prevent secondary generalisation, or at least slow seizure spread, with less devastating collapses¹⁷.

Other treatment options for refractory frontal lobe epilepsies include vagal nerve stimulation, regarded mainly as palliative treatment when focal resective surgery is not possible, and, more experimentally, repetitive transcranial magnetic stimulation (rTMS)¹⁸.

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CHAPTER 15

Occipital and parietal lobe epilepsies

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Epileptic seizures of parietal and occipital origin are heterogeneous and mainly characterised by the presenting auras, although the most dramatic clinical manifestations may reflect spread, and overshadow the focal origin. The two lobes serve mainly sensory functions, and the characteristic seizure phenomena are therefore subjective sensations. The incidence of these seizures is not well known, but they are generally considered rare. Occipital seizures have been reported to constitute 8% and parietal seizures 1.4% of total seizures in the prevalent population with epilepsy^{1,2}. The pattern of seizures is most commonly focal seizures without impairment of awareness, with occasional secondary generalisation. Focal seizures with impairment of awareness are rare and usually indicate spread of the seizure into the temporal lobe.

Seizures with somatosensory symptomatology¹⁻³

Somatosensory seizures may arise from any of the three sensory areas of the parietal lobe, but the post-central gyrus is most commonly involved. Seizures present with contralateral, or rarely ipsilateral, or bilateral sensations. All sensory modalities may be represented, most commonly tingling and numbness, alone or together. There may be prickling, tickling or crawling sensations, or a feeling of electric shock in the affected body part. The arms and the face are the most common sites, but any segment or region may be affected. The paraesthesia may spread in a Jacksonian manner, and when this occurs motor activity in the affected body member follows the sensations in about 50% of cases.

Pain is the second most common somatosensory seizure experience, often described as stabbing, intense, torturing, agonising or dull. It may be difficult to distinguish the pain from thermal perception or muscle cramps, which frequently follow the pain. Thermal perceptions are less common than pain or paraesthesia, and rarely occur without other sensory phenomena. A burning sensation is more common than the feeling of cold. Contralateral abdominal pain is also described.

A small subgroup of seizures with sexual phenomenology seems to originate in the paracentral lobule where the primary somatosensory area for the genitalia is thought to reside. The seizures present with a tactile somatosensory aura affecting the genitalia, but the ensuing seizure may exhibit other features of sexual behaviour.

A feeling of inability to move is thought to involve the secondary sensory area on the suprasylvian border. Such seizures may be preceded by a psychic aura ('psychoparetic'). Contralateral, ipsilateral, bilateral or midline structures may be affected. Paroxysmal ictal paralysis may spread in a Jacksonian way and be followed by clonic activity in the same body part. Other somatosensory features in epilepsy are body image disturbances, such as feeling of movement or altered posture in a stationary limb, feeling of floating, twisting or even disintegration of a body part. Rarely the eyes are the only affected body part, and in those cases the discharge is thought to involve the rostral

occipital cortex. Illusion of distorted or changed body shape is another phenomenon, in which a body part may be felt to be swollen or shrunken (macro- and microsomatognosia), or elongated or shortened (hyper- and hyposchematica). The peripheral parts of the extremities and tongue are most commonly affected. Other described disturbances are unilateral asomatognosia - where absence of a body part, limb or the hemibody is experienced - and sensation of a supernumerary or phantom limb. Some parietal seizures may resemble panic attacks.

Parietal onset seizures are great imitators and may, for example, give rise to hypermotoric seizures, that would more commonly be associated with the frontal lobe, and reflect the rapid anterior propagation to the parts of the brain that generate these symptoms⁴.

It is important to note that there is also sensory representation in the posterior insula and in the supplementary motor area, so seizures involving these parts may have prominent sensory symptoms⁵. Awareness of this is crucial when surgical treatment is being considered.

Seizures with visual symptomatology^{1,3}

Seizures from the occipital lobes and the parieto-occipital junction are characterised by visual phenomena, but visual auras may occur in epilepsy affecting any part of the visual pathways. Elementary visual hallucinations are most common, especially crude sensations of light or colours, which may take various shapes, be continuous, steady or moving, or be interrupted flashes of light. Visual loss, either total or partial, may also occur and is especially common in children. Transient amaurosis as an ictal phenomenon lasts seconds to minutes, but visual loss may also occur as a post-ictal deficit. Amaurosis is usually bilateral and may take the form of a blackout or whiteout.

Formed visual hallucinations are experienced fairly often in epilepsy. Pictures of people, animals or scenes may be perceived, either static or moving. One subtype is epileptic autoscopia, where the subjects see mirror images of themselves. Formed hallucinations are usually brief, and may be associated with slow head and eye turning, with the gaze towards the direction of the moving images perceived. They may be associated with various types of visual illusions. Usually, patients are aware of the unreality of the experience. In comparison with migraine, that is usually associated with sharp lines and fortification spectra, the visual hallucinations of occipital seizures commonly comprise coloured blobs of light. As a further distinction, the visual aura of migraine usually evolves much more slowly, over several minutes.

Visual illusions also occur as a seizure phenomenon, and visuo-spatial perceptions and topographical sense have been located to the non-dominant parietal lobe. The simplest types mainly involve visual illusion of spatial interpretation, illumination or colouring of vision, or movement in space. Perceived objects may appear diminished or enlarged (micro- or macropsia), altered in shape, squeezed or compressed from above, downwards or sideways, vertical and horizontal components may be oblique and lines wavy. Lines may be defective or fragmented, stationary objects seen as moving, or motion appears too slow or too fast. In some cases, such experiences may be difficult to distinguish from the characteristic illusion of movement in vertigo. More complex forms include inappropriate orientation of objects in space, like teleopsia, where objects appear both small and at a distance, or enhanced stereoscopic vision, in which near subjects seem very close and more distant objects located very far away. Palinopsia, or visual perseveration, in which visual images recur or persist after removal of the stimuli, may also occur as a seizure. The unusual nature of some events may lead to initial misdiagnosis as non-epileptic seizures.

Other seizure phenomena from occipital and parietal regions^{1,3}

Ictal anosognosia, apraxia, acalculia, alexia and aphemia may occur in epilepsy from the posterior brain regions, often presenting as confusional states. Gustatory seizures sometimes have their

origin on the suprasylvian border close to the sensory region for the mouth and tongue. Vertiginous sensations are also thought to originate in the suprasylvian and possibly the occipito-parietal region. Various seizure types may occur in a single patient at different times.

The only primary motor seizures from the posterior brain regions are oculotonic and oculoclonic seizures, or epileptic nystagmus, originating in the occipito-parietal cortex. The nystagmus usually has the fast beating component to the site opposite the lesion or EEG focus, i.e. contraversive. The nystagmus may occur as an isolated manifestation, or be associated with head or trunk version, but rarely other motor activity accompanies, and consciousness is usually retained. Eyelid flutter and rapid blinking are other features of occipital epilepsy, often at the very beginning of seizures.

Provoking and associated/accompanying features¹

Partial occipito-parietal seizures may be provoked by various stimuli involving the receptive, interpretive and connective function of the parietal and occipital lobes. The most common precipitating factor is photic stimulation, but other well-known inducers are tactile stimulation, reading, drawing, calculation and other mental activity. The EEG may show generalised changes, but focal electrical discharges in the posterior regions may occur. These seizures are very rare.

Seizure spread from an occipital or parietal origin may cause a variety of motor activities; some patients may have different patterns of seizure spread in different seizures, misleadingly suggesting multifocal disease.

Post-ictal phenomena associated with parietal and occipital seizures are transient numbness, inability to move despite no loss of power in affected limbs and post-ictal blindness. There is no correlation between duration and severity of seizures and the duration of the post-ictal neurological deficits. Post-ictal numbness and paralysis are usually short lasting, but post-ictal blindness may be prolonged and, in some cases, permanent. Fixed hemianopia may help confirm occipital lobe onset.

Causes

In a large series of patients with parietal lobe epilepsy from the Montreal Neurological Institute^{6,7}, causes included tumours, gliosis, scarring malformations, vascular lesions and infarctions. In occipital lobe epilepsy, three-quarters of patients may have underlying abnormalities shown on MRI. Causes include tumours, trauma, malformations (focal cortical dysplasia, periventricular heterotopia, band heterotopia and polymicrogyria), ischaemia, mitochondrial disease (with migraine, photosensitivity and other neurological manifestations), Sturge-Weber syndrome and coeliac disease with bilateral occipital calcifications. Occipital seizures can occur in hyperglycaemia and pre-eclampsia, and may occur early in the course of Kuf's disease or Lafora body disease. Subsyndromes of occipital epilepsy have been described in childhood and adolescence⁸⁻¹¹.

Panayiotopoulos type begins between 15 months and 17 years. Seizures are infrequent and typically occur at night, shortly after the child falls asleep. Episodes usually last less than 10 minutes and may include vomiting and gazing toward one side, and frequently evolve to rhythmic muscle contractions on one or both sides of the body. Triggers may include turning off lights, going from lighted areas to dark ones, or from dark areas to light ones.

Gastaut type begins between the ages of 3 and 16 years and has a peak onset between ages 7 and 9. Children may experience visual hallucinations with the seizure. Headaches are common before, during, or after the seizures. The prognosis for benign occipital epilepsy is excellent, and 60% children remit after two to four years in the Gastaut type. The Panayiotopoulos type is relatively benign and often does not require treatment.

Seizure semiology, the occurrence of amaurosis or migraines, and reactive EEG patterns do not differentiate between idiopathic, often benign, and symptomatic occipital epilepsy. MRI will identify most symptomatic cases. The relationship between migraine and occipital epilepsy is complex⁸. The differential diagnosis may be difficult. Further, epileptic seizures may evolve from an attack of migraine, and vice versa.

Electroencephalographic features

In somatosensory epilepsy, the localisation of electrical discharges on scalp EEG often cannot be correlated with a clinical ictal pattern and the seizures are often electrically silent. EEG changes may be lateralising rather than localising. Sometimes slow activity is most prominent. The two most common EEG features observed are central parietal spike or spike-wave discharges that may be sustained during the ictus, and temporal discharges, with occasionally more posterior spread. During seizures, spread often involves the motor cortex, and the supplementary motor or speech areas of the frontal lobes. Spread to the temporal lobes is said to be rare, but has been described and reproduced by electrical stimulation. Secondary bilateral synchrony may occur.

Changes in the posterior background activity may be helpful in occipital lobe epilepsy. Occipital foci are often widespread and may move between the occipital pole and the anterior temporal lobes. Spread seems to be to the parietal and frontal regions when the discharge originates in the supracalcarine region, but to the ipsilateral temporal lobe when the epileptic activity arises in the infracalcarine cortex. Spread to the contralateral occipital lobe via the corpus callosum seems to occur late in adult cases. Electrical abnormalities may be confined to the temporal lobes, and depth electrode studies in patients with complex partial seizures have in some cases revealed an occipital origin of the epilepsy, although such origin has not been reflected in the clinical picture of the seizures or revealed by scalp EEG. Occipital onset seizures may therefore be more prevalent than previously thought.

Treatment

The medical treatment of occipital and parietal epilepsy is no different to that of other focal epilepsies. For children who do require treatment for benign occipital epilepsy, anti-epileptic drugs are generally effective.

Surgical series are less comprehensive than those in temporal lobe epilepsy. Historical series suggest 20% of non-tumoural and 75% of tumoural parietal lobe cases may be rendered seizure-free by resective surgery^{6,7}. These figures will probably improve with the application of modern neuroimaging methods and better case selection. Surgical outcome in refractory occipital lobe epilepsy depends largely on the underlying pathology. Outcome is better for tumours than for developmental abnormalities¹². The occurrence of many types of aura in the same individual does not preclude a good surgical outcome¹³.

Surgery to the parietal and occipital lobes carries the likelihood of resulting in a fixed deficit, particularly a visual field defect, somatosensory or higher cognitive impairment. This must be explained carefully to the patient in the discussion of the risk-benefit ratio¹⁴⁻¹⁶.

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CHAPTER 16

Psychiatric disorders in epilepsy

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Studies have estimated that up to 50% of patients with epilepsy develop psychiatric disorders, the most common being depression, anxiety and psychotic disturbances¹. These psychiatric disturbances can be classified according to how they relate in time to seizure occurrence, i.e. ictal, peri-ictal (pre-ictal/prodromal, post-ictal) or inter-ictal. Multiple risk factors are associated with the increased risk of psychiatric problems in epilepsy which can be broadly divided into biological (e.g. type and severity of epilepsy), psychosocial and iatrogenic (antiepileptic drugs, surgery).

Ictal

Mood and behavioural changes can occur as direct manifestation of the seizures, including anxiety, depression, hallucinations. The episodes are usually brief (<1-3 minutes), stereotyped, begin and end abruptly, and can be associated with other ictal phenomena (oral, motor automatisms). They usually occur with partial seizures, simple partial (aura) or complex partial seizures but can also occur in generalised seizures.

Ictal anxiety is common, with up to one-third of patients with partial seizures reporting fear as part of their aura, usually in patients with right temporal foci.

Ictal depression occurs less frequently than ictal anxiety and common symptoms are guilt, hopelessness, worthlessness, and suicidal ideation.

Ictal psychotic symptoms can manifest as visual, gustatory or auditory hallucinations and are usually not well defined. They are mainly associated with partial seizures.

Ictal aggression is very rare and mostly involves undirected or unintentional violence.

The treatment of ictal psychiatric disturbances is aimed at adequate seizure control. During an episode, maintaining the patient's safety is the primary concern. Educating patients and their families about the psychiatric manifestations is also important.

Peri-ictal

Pre-ictal or prodromal mood changes usually manifest as irritability, lability, depression, anxiety or aggression and are relieved by the seizure. These symptoms can last a few hours, and sometimes up to a few days before a seizure.

Post-ictal psychiatric disturbances are more likely to occur following clusters of seizures, generalised seizures or status epilepticus.

Post-ictal confusion is characterised by impaired awareness/consciousness and diffuse EEG slowing without ictal discharges. These episodes are usually brief and common after complex partial or generalised tonic-clonic seizures. Aggressive behaviour may occur and is usually undirected or resistive and the patient is likely to be amnesic for the event.

Post-ictal mood disturbances include depression, anxiety or mania. Post-ictal depression can last longer (up to two weeks) than other post-ictal states. Symptoms range from mild to severe and may involve suicidal behaviour. It has been reported to occur more commonly with right-sided temporal or frontal foci². Post-ictal anxiety symptoms are less common. There are a few case reports of post-ictal mania characterised by symptoms of overactivity, irritability, and disorganised or disinhibited behaviour, which tend to be brief in duration.

Post-ictal psychosis

The prevalence has been estimated to be 6-10% in patients with epilepsy, particularly temporal lobe epilepsy³. It typically occurs after a cluster of complex partial seizures (+/- secondary generalisation). There is usually a period of lucidity (12-72 hours) prior to the onset of psychosis. The psychotic symptoms include delusions, hallucinations, thought disorder or mania, which are usually transient but can last several weeks. It has also been reported that some patients with recurrent episodes of post-ictal psychosis may develop an inter-ictal psychosis⁴. Predisposing risk factors are ictal fear, bilateral epileptic foci or gross structural lesions. Mechanisms are unknown but may be related to transient neurochemical changes as a result of seizures, e.g. dopamine hypersensitivity or GABA-related mechanisms.

Treatment of acute post-ictal psychosis may require short courses of benzodiazepines or antipsychotics. Improving seizure control would be the long-term goal.

Inter-ictal

Depression

Research has shown that nearly 40% of patients studied in tertiary epilepsy centres had major depression and therefore it is the commonest psychiatric disorder seen in epilepsy⁵. The true prevalence of depression in epileptic patients in the community has not been established. It is reportedly more common in patients with temporal lobe epilepsy than in generalised epilepsy. The clinical features of major depression include persistent low mood, anhedonia, loss of interest and biological symptoms of sleep or appetite disturbance. However, it is important to recognise that some patients can present with atypical depressive symptoms, referred to as inter-ictal dysphoric disorder⁶. This is characterised by chronic intermittent dysthymia, irritability and anxiety symptoms.

Treatment for depression includes psychological interventions such as counselling, psychotherapy or cognitive/behaviour therapy if appropriate. For moderate to severe depression, antidepressant medications can be prescribed. The potential risk of SSRIs lowering seizure threshold is low (greater risk with tricyclics). Electroconvulsive treatment can be effective for severe medication-resistant depression but there is a small risk of increasing seizures.

Inter-ictal anxiety disorders

The incidence of inter-ictal anxiety disorders is greater than in the general population. Panic disorder, generalised anxiety, agoraphobia, social phobia and obsessive compulsive disorder (rare) can occur. They are reportedly more common in patients with temporal lobe epilepsy, especially with left-sided foci. It is important to exclude other medical causes, e.g. thyroid, endocrine, medication effects, etc. Psychosocial difficulties, social stigma and unpredictable seizures may also contribute to anxiety symptoms.

Inter-ictal bipolar disorder

The prevalence of this is low (<5%) and characterised by periods of depressed mood and episodes of mania. Several case series have reported a preponderance of patients with complex partial epilepsy, particularly with right-sided foci.

Inter-ictal psychosis

The prevalence is reported to be 4-10% in patients with epilepsy, mainly in those with temporal lobe epilepsy^{7,8,9}. It is a chronic disorder and clinically resembles chronic schizophrenia (symptoms of delusions, hallucinations, thought disorder) but there are some reports that personality is better preserved. The onset of the psychosis is variable but usually occurs after many years of epilepsy (more than ten years). The risk factors that have been reported are early age of onset of epilepsy, bilateral temporal foci and a refractory course. It has been more commonly associated with left-sided epileptic focus^{10,11}. The pathophysiological mechanisms of psychosis in epilepsy are unclear and both focal and generalised brain abnormalities have been implicated¹²⁻¹⁵.

Treatment with antipsychotic medications is usually long term. The atypical antipsychotic drugs are potentially less likely to reduce seizure threshold (with the exception of clozapine) or cause extrapyramidal side effects. Lower doses than those used in primary schizophrenia seem to be effective. Psychosocial support and family education are also important.

Treatment-related psychiatric problems

Antiepileptic drugs

Some antiepileptic drugs (AEDs) can cause psychiatric problems, most commonly depression, anxiety, behavioural or cognitive problems and, in rare cases, psychosis. Phenobarbitone, primidone, tiagabine, topiramate, vigabatrin and felbamate have been associated with depression. Psychosis is a rare complication of a number of AEDs such as vigabatrin and topiramate.

Improved seizure control has been associated with the emergence of psychiatric symptoms. Landolt introduced the term 'forced normalisation' which refers to a dramatic reduction in epileptiform activity on EEG being associated with the emergence of psychosis or sometimes behavioural/mood disturbances. This phenomenon has been reported with most AEDs and therefore any new drug should be started at low doses and increased slowly. The risk may be higher in patients who are on polytherapy, become seizure free abruptly, or if there is a past psychiatric history.

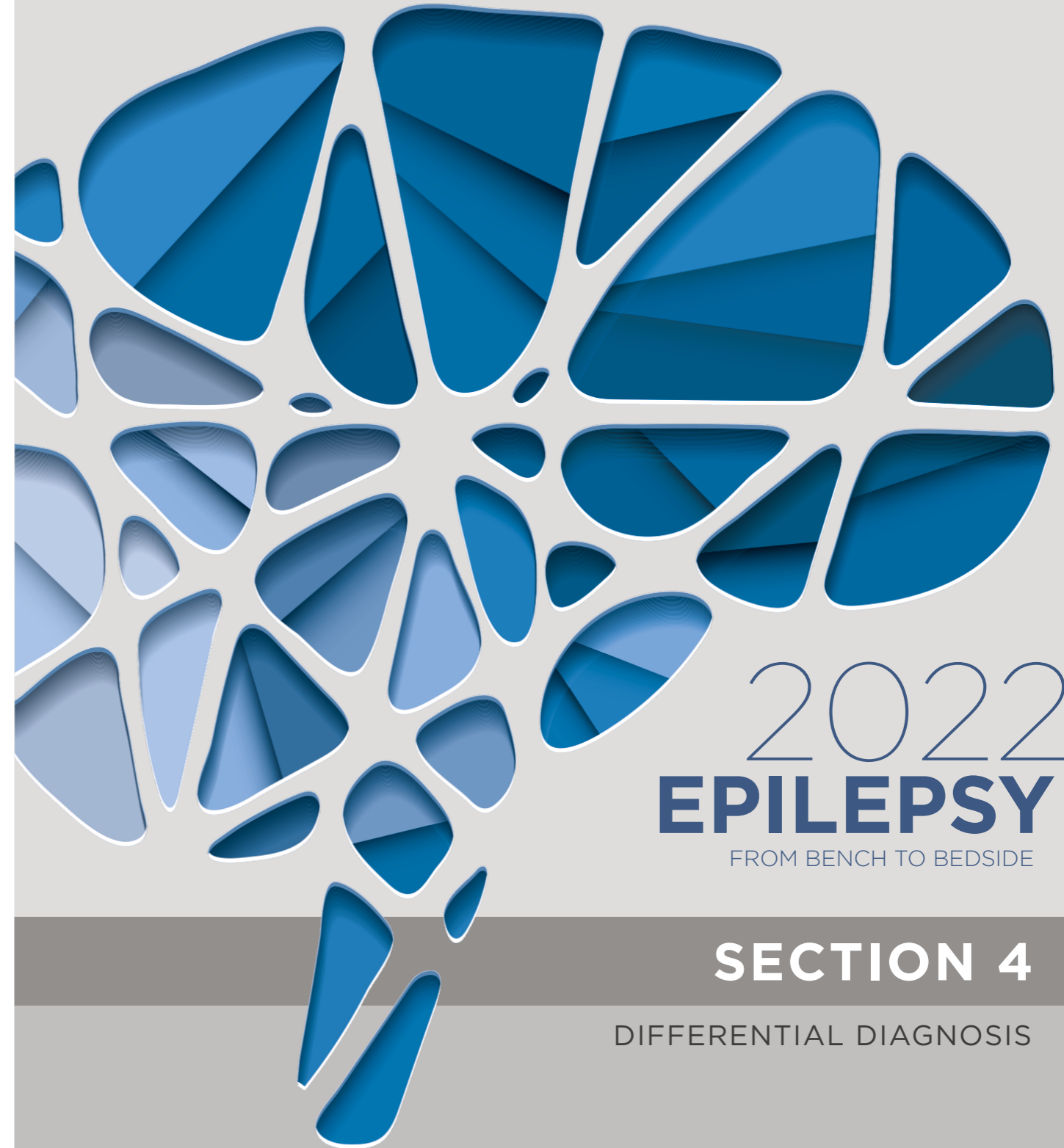
Epilepsy surgery

Transient mood disturbances (emotional lability, depression and anxiety) have been reported following temporal lobe surgery for epilepsy (about 25%) in the first 6-12 weeks¹⁶. However, in some patients (10%), symptoms, particularly depression, may persist and require psychiatric treatment. There are also reports of *de novo* inter-ictal psychosis arising after surgery. It is therefore important for pre- and post-surgical psychiatric evaluation to form part of the assessment/management for epilepsy surgery.

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EPILEPSY
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SECTION 4

DIFFERENTIAL DIAGNOSIS

CHAPTER 17

Non-epileptic paroxysmal neurological and cardiac events: the differential diagnosis of epilepsy

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An accurate clinical diagnosis requires differentiation between epilepsy and other causes of transient neurological disturbance and collapse, but the manifestations of epileptic seizures are diverse and there are many imitators, ranging from convulsive syncope to parasomnias. Nevertheless, the diagnosis of epilepsy is frequently straightforward, particularly when precise and detailed personal and eyewitness accounts of the prodrome, onset, evolution and recovery period after the event are obtained.

Misdiagnosis is common, however, and possibly affects up to 2–30% of adults with a diagnosis of epilepsy^{1,2}. For example, 74 patients previously diagnosed with epilepsy were investigated with tilt-table testing, prolonged electrocardiogram (ECG) monitoring, blood pressure and ECG-monitored carotid sinus massage and found an alternative, cardiological diagnosis in 31 patients (41.9%), including 13 taking antiepileptic medication³.

This and other reports highlight the high rate of misdiagnosis of epilepsy, the cause of which is undoubtedly multifactorial. The reasons for misdiagnosis may include a deficiency of relevant semiological information obtained during the ascertainment of the clinical history, lack of understanding of the significance of specific clinical features and over-reliance on the diagnostic value of routine investigations.⁴ Walton Centre for Neurology and Neurosurgery, Fazakerley, Liverpool L9 7LJ, UK. The attainment of a correct diagnosis is of paramount importance as an erroneous diagnosis of epilepsy has physical, psychosocial⁵ and socioeconomic consequences for the patient, and economic implications for the health and welfare services⁶.

Syncope

Transient loss of awareness is common, and may affect up to 50% of people at some stage of life^{7–9}. Elucidating the aetiological basis for an episode of loss of awareness is challenging. Typically, the episode is transient, patients are generally unable to provide an accurate description of the event and there may be a lack of reliable witnesses, particularly in the elderly who, more frequently, live alone. The difficulty in establishing an accurate diagnosis is further hampered by systemic and neurological examinations and subsequent investigations frequently being normal after an episode or between habitual attacks when the patient is seen in the hospital ward or clinic¹⁰.

Transient loss of awareness has three main underlying mechanisms:

1. Transient global cerebral hypoperfusion, i.e. syncope
2. Epilepsy
3. Dissociative (psychogenic, non-epileptic) seizures (discussed in Chapter 19).

Syncope, derived from the Greek 'syn' meaning 'with' and 'kopto' meaning 'I interrupt', may be defined as transient, self-limited loss of consciousness, usually leading to collapse, due to cerebral hypoperfusion¹¹. Syncope is more prevalent than either epilepsy or dissociative (psychogenic) seizures and is common across all age groups with an overall incidence of 10.5% over a 17-year period¹². Vasovagal syncope is most frequently encountered in adolescence, whereas syncope due to cardiac causes becomes increasingly prevalent with advancing age. The annual incidence of syncope in the elderly population in long-term care has been reported to be as high as 6%⁹. Recurrence is not unusual, occurring in approximately 30% of patients, typically within the first two years after symptom onset¹³. Recurrence is associated with increased morbidity, such as fractures, subdural haematomas and soft-tissue injuries¹⁴, and impaired quality of life¹¹.

There are numerous causes of syncope, each resulting in inappropriate systemic hypotension and critical cerebral hypoperfusion. The causes can be divided into two main groups, cardiac and vascular.

Cardiac conditions that cause syncope may be either structural heart disease, such as aortic stenosis, hypertrophic cardiomyopathy, right ventricular dysplasia, some forms of congenital heart disease, severe ischaemic cardiomyopathy and left atrial myxoma, or arrhythmias, such as ventricular tachycardia, ventricular fibrillation, Brugada syndrome, long-QT syndrome, supraventricular tachycardia, atrioventricular block, and sinus node disease causing bradyarrhythmia or asystole. Vascular causes include reflex syncope, such as neurocardiogenic or carotid sinus hypersensitivity, situational syncope, for example, during coughing¹⁵ or micturition, and postural syncope, including orthostatic hypotension or postural orthostatic tachycardia syndrome (POTS).

Neurocardiogenic syncope

Neurocardiogenic syncope is the most common cause of syncope¹¹ and has many synonyms including vasovagal, reflex, vasodepressor and neurally mediated hypotension. It arises through the provocation of inappropriate reflex hypotension, with a variable degree of bradycardia, or even transient asystole. There is often a precipitating cause such as prolonged standing in a warm environment, or fright, for example, venepuncture or the sight of blood. There may be a family history of 'fainting' or recent addition of vasoactive medication targeted at, for example, hypertension or ischaemic heart disease.

A typical attack commences with prodromal symptoms of nausea, clammy sweating, blurring or greying visual impairment, lightheadedness, and ringing or roaring tinnitus. Occasionally, visual and auditory hallucinations can be more complex, and involve figures or scenes¹⁶. Many of these individual symptoms are difficult for patients to describe and their description may be vague, but collectively the cluster of symptoms is characteristic. Subsequently, the patient will look pale and be sweaty. Mydriasis, tachypnoea, bradycardia and acral paraesthesia may be present. Muscle tone is reduced, causing the eyes to roll up, and the patient to fall to the ground. In the horizontal position, skin colour, pulse and consciousness usually return within a few seconds, and while the patient may feel briefly unwell, confusion, amnesia and drowsiness are not prolonged. Injury and incontinence are rare but may occur. Tongue biting in syncope of any cause is unusual, but frequently seen in epilepsy. The presence of brief myoclonic jerks during a syncopal episode of any cause, observed in approximately 15% of patients^{17,16}, is often over-interpreted by witnesses, and occasionally health professionals, leading to diagnostic confusion. Such myoclonic jerks are usually multi-focal and are rarely rhythmic, prolonged or of large amplitude. Videotelemetric monitoring shows that the myoclonic jerks rarely last longer than 15–20 seconds¹⁶ and do not have an EEG correlate, unlike true epileptic myoclonus. Rarely, manual and orofacial automatisms may occur, even during the presyncopal stage¹⁸. If recovery from cerebral hypoperfusion is delayed, for example if the patient is held in an upright position, a secondary anoxic convulsive seizure may occur. These should not be classified as epileptic however.

Orthostatic syncope

Orthostatic syncope is caused by autonomic failure rather than an exaggerated and inappropriate but essentially normal physiological response, as seen in neurocardiogenic syncope. Patients lose the normal vasoconstrictor response to standing, resulting in venous pooling and a postural fall in blood pressure, usually within seconds or minutes of becoming upright. Unlike in neurocardiogenic syncope, the skin stays warm and well perfused, the pulse rate is unchanged and sweating is absent. The causes of autonomic dysfunction are varied and include autonomic neuropathy due to diabetes, alcohol, amyloidosis, genetic abnormalities or complex autonomic failure, such as primary autonomic failure or multiple system atrophy. Medications such as antihypertensives, phenothiazines, tricyclic antidepressants, diuretics and medication for Parkinson's disease may also be implicated.

Postural orthostatic tachycardia syndrome

Postural orthostatic tachycardia syndrome (POTS) is an autonomic disturbance characterised by symptoms of orthostatic intolerance, mainly light-headedness, fatigue, sweating, tremor, anxiety, palpitation, exercise intolerance and syncope or presyncope on upright posture¹⁹. Patients also have a heart rate greater than 120 beats per minute on standing or an increase in heart rate of 30 beats per minute from a resting heart rate after standing for 1–5 minutes, compared to an increase of only 15 beats per minute in heart rate in the first minute of standing in normal subjects. POTS is most common in females between the ages of 12 and 50 years and may follow surgery, pregnancy, sepsis or trauma²⁰. The pathophysiological basis of POTS is not well understood. Hypotheses include impaired vascular innervation, baroreceptor dysfunction and high plasma noradrenalin concentrations, of which impaired innervation of the veins or their response to sympathetic stimulation is probably the most important²¹.

Carotid sinus hypersensitivity

Carotid sinus hypersensitivity (CSH) is an exaggerated response to carotid sinus baroreceptor stimulation. Even mild stimulation to the neck results in presyncopal symptoms or syncope from marked bradycardia and a drop in blood pressure causing transiently reduced cerebral perfusion. CSH is found in 0.5–9.0% of patients with recurrent syncope and is observed in up to 14% of elderly nursing home patients and 30% of elderly patients with unexplained syncope and drop attacks^{22,23}. It is more common in males. It is associated with an increased risk of falls, drop attacks, bodily injuries, and fractures in elderly patients but rates of total mortality, sudden death, myocardial infarction, or stroke are similar to the general population. Around 30% of cases are classified as cardioinhibitory where the predominant manifestations are sinus bradycardia, atrioventricular block, or asystole due to vagal action on sinus and atrioventricular nodes. Permanent pacemaker implantation is effective at reducing recurrence rate²⁴. The vasodepressor type also comprises 30% of cases and results in a marked decrease in vasomotor tone without a change in heart rate. The remaining patients are of a mixed type²⁵. Untreated symptomatic patients have a syncope recurrence rate as high as 62% within four years. The diagnosis is established by performing carotid sinus massage with the patient supine, under ECG and blood pressure monitoring.

Cardiogenic syncope

Cardiogenic syncope arises from either a rhythm disturbance or structural cardiac defects. The identification of a cardiac cause of syncope is of paramount importance because the prognosis is poor if untreated^{10,13,26,27}. A family history of sudden cardiac death may be present, indicating the possibility of Brugada syndrome, long-QT syndrome or an inherited cardiomyopathy, for example, hypertrophic cardiomyopathy, familial dilated cardiomyopathy or arrhythmogenic right ventricular dysplasia. Typically, presyncopal symptoms will be absent, and the circumstances of the syncope may be important. Syncope *after* exercise is a manifestation of neurocardiogenic syncope, whereas

syncope *during exercise* is more suggestive of cardiomyopathy or primary electrical disturbance such as Wolff-Parkinson-White syndrome or right ventricular dysplasia.

Cerebrogenic cardiac dysfunction has also been observed. Arrhythmias, conduction block, and repolarisation ECG abnormalities have been reported in up to 56% of epileptic seizures. Abnormalities appear to be more common in nocturnal, prolonged, and generalised seizures than in focal seizures or those occurring during wakefulness²⁸⁻³².

Differentiation

The differentiation between epileptic seizures and syncopal attacks can be difficult. Typically, patients with epilepsy have more episodes of loss of consciousness and a longer history than patients with syncope. Clinical features that are most strongly predictive of syncope of any cause versus seizures are a postural component, a prior history of presyncopal episodes with unpleasant situations, diaphoresis, dyspnoea, chest pain, palpitations, a feeling of warmth, nausea, and vertigo. Patients are also more likely to have hypertension and ischaemic heart disease.

In a study evaluating the utility of a diagnostic questionnaire, epilepsy was predicted by the presence of tongue biting, urinary incontinence, prodromal déjà vu, post-ictal confusion, mood disturbance, muscle pain, headaches, witnessed convulsive movements, head turning and cyanosis¹⁷. The application of the questionnaire resulted in a diagnostic accuracy of 86%, suggesting that the careful evaluation of the history from the patient and witness is of principal importance in attaining the correct diagnosis. It is important to note that syncope due to primary cardiac disease may present with sudden collapse and have a less well defined, or often completely absent, prodromal period compared to vasovagal syncope^{18,16,33}.

In patients with syncope, neurological and cardiological examinations are frequently unrewarding. Further investigations may be necessary and are dependent on the history obtained. Extensive investigation is not mandatory, however, in patients with, for example, a typical history of neurocardiogenic syncope. A 12-lead ECG should, however, be undertaken in all patients. Patients with an abnormal cardiological examination or 12-lead ECG or those patients with a family history of sudden cardiac death or a personal history that is atypical for neurocardiogenic syncope, for example, episodes during exercise, while lying flat or with palpitations, warrant more extensive cardiac investigations including a transthoracic echocardiogram, prolonged ECG monitoring and, frequently, tilt-table testing.

In conditions such as Brugada syndrome, the ECG abnormalities may be intermittent. Serial ECGs in undiagnosed syncope may, therefore, be helpful. In patients with infrequent episodes, one- to seven-day prolonged, Holter-type, ECG recordings have a yield of less than 1%¹¹ and implantable loop recorders, which can monitor cardiac rhythm for up to 18 months, are more appropriate, with a yield in unexplained syncope of up to 50%³⁴⁻³⁶. Autonomic function testing, and more specifically tilt-table testing (for example, 70° tilt for 45 minutes) also has high sensitivity (approaching 70%) for identifying patients with a syncopal tendency, particularly in patients over the age of 50 years with recurrent syncope and no structural cardiac pathology^{37,38}, but reproducibility has been reported to be poor³⁹. Measures to induce syncope, such as isoprenaline, provoke syncope more rapidly and provide additional sensitivity (10-15%), but at the expense of reduced specificity⁴⁰.

Prognosis and treatment

The prognosis and treatment of syncope is entirely dependent on the underlying aetiology. Structural heart disease significantly increases the risk of death in patients with syncope¹¹. For example, patients with syncope and severe left ventricular failure have a one-year mortality rate of 45% compared to a similar group of patients with cardiac failure but no syncope^{10,26,27}. In contrast,

patients with neurocardiogenic syncope, aged 45 years or less, without structural heart disease have no increase in mortality rate. Even patients who remain undiagnosed following extensive investigations have a good prognosis^{10,13}. It is therefore of paramount importance, from a prognostic and interventional point of view, to identify those patients with syncope due to an underlying cardiac cause.

Drop attacks

Neurological causes of sudden collapse other than epilepsy and autonomic dysfunction include intermittent obstructive hydrocephalus caused by, for example, a colloid cyst of the third ventricle or a craniocervical junction abnormality such as an Arnold-Chiari malformation. Colloid cysts present with syncope and sudden death, particularly with changes in posture, are readily identified on neuroimaging and are amenable to neurosurgical intervention^{41,42}.

Diencephalic attacks, as sequelae of diffuse brain injury, are extremely rare and manifest as autonomic dysfunction with diaphoresis, sinus tachycardia, collapse and intermittent hypertension⁴³.

Brainstem and spinal cord lesions or lower limb weakness of any cause may present with unexplained falls without impairment of consciousness. There are usually fixed neurological signs which will guide appropriate investigations and the episodes are rarely confused with atonic or tonic seizures of epilepsy. Cataplexy usually occurs in association with the narcoleptic tetrad of excessive daytime somnolence, hypnagogic hallucinations, and sleep paralysis, although it may be the presenting feature. Further details regarding this condition are found in Chapter 18 on epilepsy and sleep.

Idiopathic drop attacks are most commonly seen in middle-aged women. They take the form of a sudden fall without loss of consciousness, and patients frequently remember hitting the ground. Recovery is instantaneous but injury often occurs. Neurological, cardiac and autonomic investigations are unrewarding.

It is likely that vertebrobasilar ischaemia is overdiagnosed and probably accounts for only a small proportion of drop attacks. Typically, the attacks occur in the elderly, with evidence of vascular disease and cervical spondylosis, both commonly occurring conditions which frequently co-exist in the elderly population. Furthermore there is clinical overlap with other more commonly occurring but benign conditions such as benign paroxysmal positional vertigo. The attacks may be precipitated by head turning or neck extension resulting in distortion of the vertebral arteries and haemodynamic ischaemia, although embolic events are probably a more frequent cause. Drop attacks are accompanied by features of brainstem ischaemia such as diplopia, vertigo and bilateral facial and limb sensory and motor deficits⁴⁴.

Hyper- and hypokalaemic periodic paralyses (PP) are rare autosomal dominant disorders of sodium and calcium ion channel dysfunction characterised by episodic flaccid weakness secondary to abnormal sarcolemmal excitability and rapid changes in serum potassium levels. Cranial musculature and respiratory muscles are usually spared. Attacks last from between minutes in hyperkalaemic PP to hours and occasionally days in hypokalaemic PP. Precipitants include fasting, alcohol, resting following exercise, stress (hyperkalaemic PP) and a high carbohydrate meal, cold and exertion the previous day (hypokalaemic PP). Acute treatment is directed at supportive care and normalisation of the serum potassium. Effective prophylaxis of hypokalaemic PP, like many of the channelopathies, is with acetazolamide⁴⁵. Thyrotoxicosis is the commonest cause of secondary periodic paralysis.

Convulsive movements and transient focal hypermotor episodes

Convulsive limb movements commonly accompany episodes with transient loss of awareness and are most commonly due to epilepsy, syncope or dissociative seizures. Transient, episodic limb movements without loss of awareness are also frequently misdiagnosed as epilepsy. There is often a degree of overlap with myoclonus as the clinical manifestation of a variety of pathophysiological processes embracing the subspecialty fields of both epilepsy and movement disorders. Epileptic myoclonus, which is cortical in origin, can be confused with other hyperkinetic movement disorders, including myoclonus originating from subcortical structures, brainstem, spinal cord or peripheral nerves, tics, chorea, dystonia and tremor. Definitive localisation of the myoclonic focus requires electrophysiology, specifically a time-locked back-averaged EEG. Careful neurological examination is also often helpful in this regard, for example, in identifying spinal cord pathology or evidence of a cortical process.

Cortical myoclonus arises from a hyperexcitable focus within the sensory-motor cortex, and involves an arm, leg or the face. In general, it is typically arrhythmic, although in the setting of *epilepsia partialis continua* jerks may appear rhythmic. Cortical myoclonus is triggered by action or intention, and is often stimulus-sensitive. Subcortical myoclonus refers to myoclonus without a preceding cortical discharge and arises from structures such as the thalamus, and is usually, although not exclusively, stimulus-insensitive. In practice, it is frequently difficult to differentiate cortical from subcortical myoclonus on clinical grounds, and neurophysiological investigation is required. Neuroimaging may also be helpful in this regard. Myoclonus arising from the brainstem (startle, palatal and reticular reflex myoclonus), spinal cord (segmental and propriospinal myoclonus) and peripheral nerves are usually recognised and differentiated from epilepsy without difficulty.

Among the hyperkinetic movement disorders, tremor is the entity most often confused with myoclonus and convulsive limb movements. Tremor is habitually rhythmic and oscillatory, and significantly slower than myoclonus; however, occasionally tremor may be jerky and irregular, mimicking clonic jerks to the degree that electrophysiological investigation is required to differentiate between them.

Like myoclonus, tics are also brief; however, they are typically preceded by an urge to perform the movement and can usually be temporarily suppressed, features not seen in myoclonus or simple partial seizures. Tics are usually stereotyped, repetitive and often complex, involving multiple different non-contiguous muscle groups.

Chorea, a brief involuntary 'dance-like' movement, is usually easy to distinguish from myoclonus and epilepsy due to the characteristic flowing movements. Dystonia is an involuntary movement disorder characterised by repetitive, sustained movements that typically produce twisting postures. Dystonia rarely mimics myoclonus although it may be confused with epileptic tonic spasms or the dystonic posturing seen in partial seizures of frontal or temporal lobe origin. Many patients with dystonia possess a manoeuvre that attenuates the dystonia, termed a 'geste antagoniste'.

Paroxysmal dyskinesias are a genetically and clinically heterogeneous group of rare movement disorders characterised by episodic dystonic or choreiform movements. Paroxysmal kinesigenic dyskinesia (PKD) is the most common type, although the precise prevalence is unknown. This condition is characterised by brief attacks of unilateral or bilateral limb dystonia or chorea, lasting less than one minute and with preserved consciousness, triggered by initiation of voluntary movements. An 'aura', such as an unusual cephalic or epigastric sensation, may precede the attacks, further adding to the diagnostic confusion⁴⁶. Sporadic cases occur; however, PKD is considered to be an autosomal dominant condition with variable penetrance, linked to the pericentromeric

region of chromosome 16⁴⁷⁻⁴⁹. The underlying pathophysiological mechanism is thought to be a sodium channelopathy because the condition is highly responsive to carbamazepine and there is possibly some overlap with afebrile infantile convulsions and channelopathy-related epilepsies, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).

Episodic ataxias typically present in childhood or adolescence and manifest as ataxia and myokymia (type 1, potassium channelopathy) or vertigo, ataxia and occasionally syncope (type 2, calcium channelopathy). These events are commonly diagnosed as epilepsy and EEG recordings can show sharp and slow waves. Moreover, true epileptic seizures can occur, confounding the diagnosis further.

Painful tonic spasms of multiple sclerosis and other upper motor neuron disorders are involuntary, unilateral dystonic movements that are frequently precipitated by movement. The clinical history and neurological examination should usually provide sufficient evidence to differentiate between tonic spasms of, for example, multiple sclerosis, epileptic seizures and paroxysmal dyskinesias.

Startle syndromes are a heterogeneous group of disorders, comprising hyperekplexia, startle epilepsy and neuropsychiatric syndromes, which are characterised by an abnormal motor response to startling events. Despite some clinical overlap, a carefully recorded history is frequently sufficient to accurately differentiate these entities⁵⁰. Hyperekplexia is characterised by an exaggerated startle response consisting of forced closure of the eyes and an extension of the extremities followed by a generalised stiffness and collapse. It can be mistaken for cataplexy in patients with narcolepsy, or atonic or tonic epileptic seizures. More minor forms of hyperekplexia display an exaggerated startle response without tonicidity and collapse. Hyperekplexia may be hereditary, due to a genetic mutation in the alpha-1 subunit of the glycine receptor on chromosome 5, sporadic or symptomatic, secondary to widespread cerebral or brainstem damage. Clonazepam may be helpful in reducing both the severity of the startle response and degree of tonicidity⁵¹.

Startle epilepsy usually manifests as an asymmetric tonic seizure, triggered by a sudden stimulus^{52,53}. Other ictal patterns such as absences, atonic seizures, or generalised seizures are less common. EEG abnormalities during such seizures may be obscured by profuse electromyographic activity in the pericranial muscles, although occasionally epileptiform activity over the vertex may be seen. Startle-provoked seizures usually become manifest after spontaneous epileptic seizures of the same ictal phenotype have been present for a prolonged period with a high-frequency, possibly due to a kindling-like phenomenon. In the majority of cases, both ictal phenotype and neuroimaging data suggest a seizure onset zone within the supplementary motor area. Other than hyperekplexia, startle-induced conditions which may be confused with reflex startle epilepsy include stiff-person syndrome⁵⁴ and progressive encephalomyelitis with rigidity and tetanus, although the presence and nature of concomitant neurological symptoms and signs readily distinguish these conditions from each other.

Transient focal sensory attacks

Migraine and epilepsy are both characterised by paroxysmal cerebral dysfunction and a possible relationship between migraine and epilepsy has been postulated^{55,56}. Migraine is frequently mistaken for epilepsy, particularly in acephalgic migraine, when the headache is mild or absent. Epileptic seizures can be accompanied or followed by migraine-like headache⁵⁷⁻⁵⁹, and attacks of migraine can lead to unconsciousness⁶⁰, particularly in basilar migraine⁶¹, and acute confusion^{62,63}. Migraine attacks can cause epileptiform EEG abnormalities⁶⁴⁻⁶⁶, although the EEG changes are usually non-specific. It has been suggested that episodes of migraine with aura may provoke seizures, in a condition termed 'migralepsy'⁶⁷, although this has not been universally accepted⁶⁸.

Attacks of migraine and of epilepsy also have various precipitants in common, such as hormonal factors and sleep disturbance⁵⁶. A migrainous aura may have visual, sensory or motor features that may be suggestive of seizure activity and alertness may be impaired. There are, however, a number of important semiological differences. Visual migraine auras are monochromatic, angulated, bright and frequently scintillating. They commence in the centre of the visual field and gradually evolve over several minutes towards the periphery of one hemi-field, often leaving a scotoma. They usually last between 30 and 60 minutes. In contrast, simple partial seizures arising from the occipital lobe are circular, amorphous, multicoloured obscurations that develop rapidly within seconds, and are brief in duration (2–3 minutes). They often appear in the periphery of a temporal visual hemi-field, becoming larger and multiplying in the course of the seizure, while frequently moving horizontally towards the other side^{69,70}.

Somatosensory migraine commences with unilateral paraesthesias spreading from one area to another over 15–30 minutes, often resolving in the first area before becoming evident in the next. Epileptic sensory symptoms arise quickly and spread rapidly over seconds to involve other somatic areas in summation, often culminating in secondary generalisation. Peripheral neuropathies or radiculopathies also cause sensory symptoms and may be transient if, for example, they are compressive or inflammatory in aetiology. Neurological examination may reveal evidence of a fixed neurological deficit, and the circumstances in which the sensory symptoms develop and lack of associated epileptic semiology rarely result in diagnostic confusion.

Transient ischaemic attacks (TIAs) are broadly distinguished from seizures and migraine by their 'negative' symptoms, that is, sensory loss, weakness or visual impairment, with retained awareness. However, tingling and focal jerking may occur in association with local cerebral hypoperfusion and occasionally with severe bilateral carotid stenosis⁷¹.

Vertigo with brief episodes of disequilibrium is often misinterpreted as seizure activity. More commonly, the symptoms are due to disorders of the peripheral vestibular system, such as benign paroxysmal positional vertigo or Ménière's disease. Vertigo may occur as a feature of focal seizures, arising from the frontal or parietal regions and specifically the intraparietal sulcus, posterior superior temporal lobe, and the temporo-parietal border regions^{72–75}. Vertigo observed in epileptic seizures rarely occurs in isolation and other clinical manifestations of seizure activity, such as impaired awareness, are also usually present. Vertigo due to a peripheral vestibular disorder is often accompanied by nausea and vomiting and precipitated by head movement, such as rolling over in bed or on provocation with Hallpike's manoeuvre. Focal onset or generalised epileptic seizures may be provoked by the same manoeuvres in patients with 'vestibular epilepsy', a subtype of the reflex epilepsies.

Psychic experiences

Focal seizures arising from the temporal lobe commonly involve psychic phenomena, including déjà vu, panic and fear, visual, olfactory or auditory hallucinations. Perception of the environment may be altered with derealisation, micropsia and macropsia, and interaction with others may be impaired by abnormal language function and altered thought patterns, seen most commonly in temporal and frontal lobe seizures. Panic attacks, which have a psychological rather than epileptic basis, are associated with feelings of fear and anxiety, hyperventilation and palpitations. The diagnosis is usually clear as they are commonly situational rather than spontaneous, and have a protracted time course with a characteristic evolution. Simple partial seizures arising from the amygdala can, however, be difficult to differentiate from brief episodes of fear and anxiety^{76,77}.

Hallucinations or illusions can occur in the context of loss of a primary sense. This is well recognised in limb amputees, with phantom limb pain and sensory disturbance. Similarly, patients with visual impairment may develop Charles Bonnet syndrome, with visual hallucinations in the area of visual field loss. This results from damage to the visual system due to, for example, age-related macular degeneration or glaucoma, but it may also arise in patients with intracranial pathology and secondary deafferentation of the visual cortex⁷⁸.

Aggressive or vocal outbursts

Episodic dyscontrol syndrome (EDS) and its counterpart, intermittent explosive disorder (IED), are patterns of abnormal, episodic, and frequently violent and uncontrollable social behaviour often in the absence of significant provocation. These events are frequently attributed to epilepsy as they often arise seemingly out of character. Uncontrolled rage occurring in the context of epileptic seizures is also unprovoked, however the anger is usually undirected or reactive, the episodes occur in isolation and other manifestations of a seizure disorder are frequently present. Additionally, routine inter-ictal EEG recordings in EDS have not shown epileptiform activity⁷⁹. Interestingly, however, a significant proportion of patients demonstrate non-specific diffuse or focal slowing not attributable to drowsiness or the effects of medication. There is neuroimaging evidence of frontolimbic involvement in the pathogenesis of EDS and IED and co-existent neurological and psychiatric conditions are frequently seen⁸⁰. So although the rage attacks themselves may not have an epileptic basis, the two conditions may be pathogenetically linked.

Prolonged confusional or fugue states

Acute neurological conditions, such as non-convulsive status epilepticus, intracranial infections, head injuries, ischaemic events and drug intoxication or withdrawal may result in an acute confusional state. Systemic disorders may also give rise to episodes of acute encephalopathy and transient loss of consciousness such as renal or hepatic failure and endocrine and metabolic abnormalities, the most common of which is hypoglycaemia related to insulin therapy in diabetes mellitus. Other precipitants of hypoglycaemia include alcohol, insulinomas, rare inborn metabolic abnormalities, such as congenital deficiencies of gluconeogenic enzymes, and renal or hepatic disease. The symptoms of hypoglycaemia are protean, and include visual disturbance, diaphoresis, confusion, unconsciousness, and altered behaviour including irritability and aggression. Peri-oral and acral paraesthesias, ataxia, tremor and dysarthria are common features, leading to diagnostic confusion unless an accurate history and appropriate laboratory investigations are performed. The rare disorders of pheochromocytoma, carcinoid syndrome and hypocalcaemia may also present with confusion, presyncope or syncope and the hypocalcaemic sensory disturbance may be mistaken as an epileptic aura⁸¹.

Transient global amnesia (TGA) usually occurs in middle-aged or elderly people and is characterised by the abrupt onset of anterograde amnesia, accompanied by repetitive questioning⁸². With the exception of the amnesia, there are no neurological deficits. There is neither clouding of consciousness nor loss of personal identity. Attacks last between minutes and hours, with six hours being the average duration. The ability to lay down new memories gradually recovers, leaving only a dense amnesic gap for the duration of the episode and a variable degree of retrograde amnesia. The attacks are often associated with headache, dizziness and nausea. The duration and number of attacks are important in distinguishing TGA from transient epileptic amnesia and transient ischaemic events affecting mesial temporal lobe structures. Unlike the epileptic form of amnesia, TGA rarely lasts less than one hour, and recurrences occur in less than 10% of patients. The aetiological basis of TGA is uncertain. Possible underlying mechanisms include cortical spreading depression or venous congestion. Most likely, however, TGA may refer to a single expression of several pathophysiological phenomena^{82,83}.

Fugue states may also be psychogenic, as a dissociative state symptom. Inconsistencies in cognition and mental state are often elucidated if the patient is examined during an episode, which may be prolonged, lasting days or even weeks.

Summary

In conclusion, there are a large number of neurological and cardiac conditions which result in paroxysmal clinical events and although the causes are multiple and diverse, the clinical manifestations may be similar. The attainment of an accurate and detailed history from the patient and a witness is essential in differentiating these conditions. The application of appropriate investigations frequently increases clinical yield and directs apposite therapy. Nevertheless, misdiagnosis is common and may have profound physical, psychosocial and socioeconomic consequences for the patient, and economic implications for the health and welfare services.

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Table. Non-epileptic paroxysmal neurological and cardiac events.

SYNCOPE

Neurocardiogenic (*also known as vasovagal, reflex, vasodepressor syncope*)

Cardiac

Structural

- Cardiomyopathies (obstructive, dilated, restrictive, right ventricular dysplasia)
- Valvular disease (mitral and aortic stenosis and mitral valve prolapse)
- Other (atrial myxoma)

Arrhythmia

- Inherited (long-QT, Brugada and Wolff-Parkinson-White syndromes)
- Acquired (SVT, VT, atrioventricular block, sinus node disease)

Orthostatic

Autonomic failure

- Neuropathy
- Complex autonomic failure (primary, multiple system atrophy)

Postural orthostatic tachycardia syndrome

Carotid sinus hypersensitivity

Situational

- Tussive, micturition, swallowing

Neurological

- Cerebrogenic cardiac arrhythmias

Table. Continued

DROP ATTACKS

Cardiac (as opposite)

Neurological

- Cerebrospinal fluid dynamics
 - Colloid cyst of 3rd ventricle, Arnold-Chiari malformation
- Diencephalic attacks
- Lower limb weakness
 - Brainstem and spinal cord lesions and lower motor neuron disorders
- Cataplexy
- Idiopathic drop attacks
- Vertebrobasilar ischaemia
- Periodic hypo- and hyperkalaemic paralyses

TRANSIENT HYPERMOTOR EPISODES

Myoclonus

- Cortical, subcortical, brainstem, spinal cord and lower motor neuron disorders

Tics

Dystonia

Tremor

Chorea

Paroxysmal dyskinesia

- Kinesigenic, non-kinesigenic, exertion-induced, choreoathetosis with spasticity

Episodic ataxia

- Type 1 and 2

Startle syndromes

- Hyperekplexia
- Culture specific syndromes
 - Jumping Frenchmen of Maine, Latah, Myriachit
- Acquired
 - Stiff person syndrome, progressive encephalomyelitis with rigidity

Tonic spasms

- Upper motor neuron disorders
- Multiple sclerosis, cerebral palsy

Cerebral ischaemia

TRANSIENT FOCAL SENSORY ATTACKS

Migraine

Transient ischaemic attacks

Lower motor neuron disorders

- Radiculopathies, neuropathies

Vertigo

- Ménière's disease, benign paroxysmal positional vertigo

Table. Continued

PSYCHIC EXPERIENCES

Panic attacks

Loss of primary sense

- Charles Bonnet syndrome
- Post-amputation

AGGRESSIVE OR VOCAL OUTBURSTS

Episodic dyscontrol syndrome

EPISODIC PHENOMENA IN SLEEP

Sleep wake-transition disorders

- Hypnic jerks
- Rhythmic movement disorders
- Jactatio Capitis Nocturna

Restless legs syndrome

Periodic limb movements in sleep

Non-REM parasomnias

- Somnambulism, night terrors, confusional arousals

REM parasomnias

- Nightmares, sleep paralysis, REM sleep behaviour disorder

Sleep apnoea

- Obstructive
- Central

PROLONGED CONFUSIONAL OR FUGUE STATES

Encephalopathy

- Neurological
 - Intracranial infection, ischaemia, head injury
- Systemic
 - Infection, hypoxia, hypercapnia, hypoglycaemia, hypocalcaemia, hyponatraemia, hepatic and renal failure, drug and alcohol intoxication, endocrine dysfunction including thyroid disorders, pheochromocytoma, carcinoid

Transient global amnesia

CHAPTER 18

Epilepsy and sleep

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The relationship between epilepsy and sleep is complex as seizures may be exacerbated by sleep deprivation and some seizures mainly occur during sleep. Further, there is a possibility of nocturnal seizures being misdiagnosed as parasomnia and *vice versa*. Finally, sleep disorders may aggravate epilepsy and epilepsy may aggravate certain sleep disorders.

Normal sleep physiology and relationship to seizures

Sleep consists of active brain states during which many biological processes occur, such as synaptic plasticity and memory consolidation¹. Using electroencephalography (EEG) sleep can be broadly divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM can be subdivided into light (stages I/II) and deep (stage III, previously split into stages III/IV) sleep. These sleep states cycle over 90 minutes throughout the night. Deep sleep mainly occurs during the first part of the night, and towards morning there is more REM sleep (Figure 1). The transition between wakefulness and sleep and between different sleep stages is often gradual and the mechanisms controlling these transitions are poorly understood.

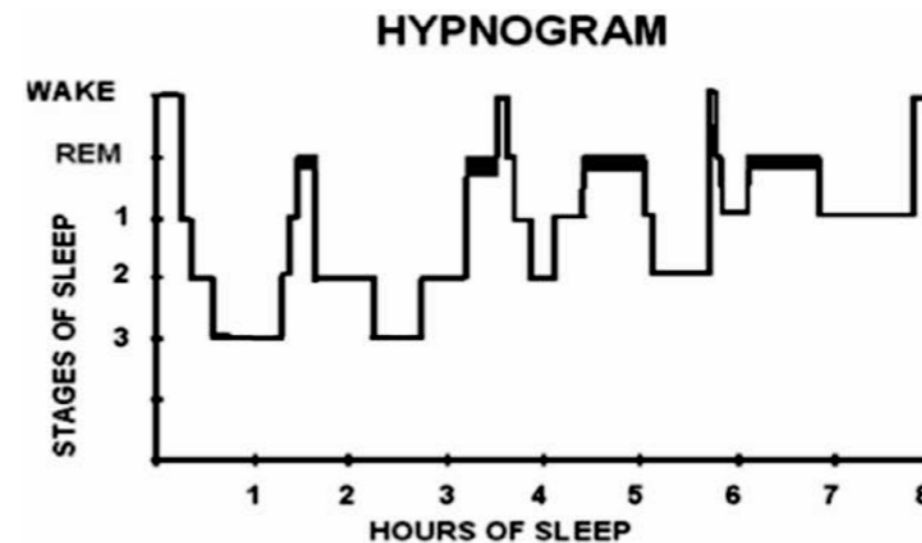


Figure 1. Normal hypnogram. Note that there is more deep sleep in the first parts of the night and more REM sleep towards morning.

It has been clear for many years that some patients with epilepsy have seizures mainly during sleep^{2,3}. Particularly, frontal lobe seizures often occur from both daytime and night-time sleep.

However, if temporal lobe seizures occur during sleep, the seizures are more likely to secondarily generalise⁴. The term Nocturnal Frontal Lobe Epilepsy (NFLE) was previously commonly used. Since the attacks are associated with sleep rather than time of day, and the seizures may arise from extra-frontal brain regions, it was recently recommended to change the name to Sleep-related Hypermotor Epilepsy (SHE)⁵. There may also be diurnal variation of certain types of epileptic syndromes such as juvenile myoclonic epilepsy or epilepsy with generalised tonic-clonic seizures on awakening⁶. Both benign (such as benign focal epilepsy with centrotemporal spikes [BECTS]) and severe epilepsy syndromes (such as Landau-Kleffner and Lennox-Gastaut syndrome with electrical status epilepticus during sleep [ESES]) show a predilection for sleep.

Thalamocortical rhythms are activated during NREM sleep giving rise to sleep spindles. Similar circuits are involved in the generation of spike-wave discharges in primary generalised epilepsy, providing a possible explanation for the promotion of spike-wave discharges seen during NREM sleep⁷.

Inter-ictal epileptiform discharges (IED) are facilitated following sleep deprivation, even in the absence of sleep during the EEG recordings⁸. The reasons for this remain unclear but it has been suggested that the increase in spike-wave activity seen after sleep deprivation may be due to more frequent fluctuations in vigilance levels both during wakefulness and sleep⁹. Using Transcranial Magnetic Stimulation (TMS), increased cortical excitability has been shown in epilepsy patients after sleep deprivation. This has not been the case for control subjects or at least not to the same extent. Interestingly, changes have been seen bilaterally in patients with generalised epilepsies but only ipsilateral to seizure onset zone in patients with focal epilepsies¹⁰⁻¹¹. Changes may reflect reduced intracortical inhibition, as the most likely mechanism for an increase in excitability at the stimulation intervals used is reduced GABA activity.

The propensity for IED as well as seizures also varies throughout the night and IED are more commonly seen during NREM sleep than REM sleep¹²⁻¹⁴. Epileptic seizures can occur at any stage of NREM sleep but are more frequent during changes between sleep stages and lighter stages than deep sleep. Seizures rarely occur during REM sleep⁴. It appears that while IED activation is principally favoured by sleep, the transition from interictal to ictal state is modulated by circadian factors related to the location of the epileptic network or epilepsy type and seizure onset zone often influences timing of the seizures¹⁵.

Interaction between sleep disorders, antiepileptic drugs and epilepsy

Excessive daytime sleepiness (EDS) is common in patients with epilepsy and is often attributed to antiepileptic medication. Tiredness is often a dose-related side effect of many antiepileptic drugs (AEDs). AEDs may, however, also interfere with the normal sleep pattern. AEDs have different effects on sleep (summarised in Table 1) and some also have different long- and short-term effects. For example, carbamazepine initially reduces and fragments REM sleep, but this effect is reversed after a month of treatment. GABAergic drugs (such as phenobarbitone and benzodiazepines) prolong NREM sleep and shorten REM sleep and gabapentin and pregabalin have been shown to increase slow-wave sleep (SWS) and have even been suggested as a treatment option for primary insomnia Pregabalin increases slow-wave sleep and may improve attention in patients with partial epilepsy and insomnia¹⁶.

Vagus Nerve Stimulator (VNS) may also influence sleep and studies have also shown that OSA may be triggered by or exacerbated by insertion and treatment with VNS¹⁷.

Seizures and frequent IED can also disrupt sleep architecture, causing more unstable sleep in both partial and generalised epilepsies. Patients with epilepsy may have increased sleep latency and number of awakenings during night, as well as reduction or fragmentation of REM sleep. Reduced amount of REM sleep has been seen after both daytime and nocturnal temporal lobe seizures¹⁸. The effect was most pronounced when seizures occurred during sleep but also significant when seizures occurred on the previous day. Disrupted sleep may hence contribute to the prolonged recovery time that some patients report following seizures. Polysomnography of patients with Juvenile myoclonic epilepsy (JME) have also shown reduced sleep efficiency and increased sleep latency, unrelated to seizures as well¹⁹.

Obstructive sleep apnoea (OSA) is more common in patients with epilepsy than in the general population and may be related to severity of epilepsy. The risk factors for OSA are however the same as in the general population (male gender, obesity, age). OSA may fragment sleep as well as cause sleep deprivation that may have detrimental effect on seizure control. In older adults with late onset seizures or worsening of seizure control, OSA has been associated with seizure exacerbation²⁰. Several studies have also shown an improvement of seizure control after treatment of concomitant OSA²¹⁻²⁴.

Patients may be amnesic for events but often describe dream-like experiences such as seeing spiders, feeling chased, and house/walls collapsing on them. These events are not as narrative as dreams associated with REM sleep. Events may also be related to daytime frustrations or events. The bed partner may describe fearfulness or confusion and patients may get out of bed with these events. These conditions are most common in children (up to 20% of children sleep walk). Symptoms may also occur in adults, up to 2-3% are said to have events at least 1/year²⁹. There is often a history of NREM parasomnias in childhood but NREM parasomnias may also start in adulthood.

The similarities between features seen during NFLE and NREM parasomnias have prompted the hypothesis that the disorders may have a common pathogenic background³⁰. Central pattern generators (CPGs) are neuronal networks activating specific sequences of motor responses. These are usually controlled by the cortex, but temporary loss of this control, either by sleep or epilepsy, facilitated by arousal, can result in the emergence of stereotyped inborn fixed action patterns seen in both NFLE and NREM parasomnias³⁰⁻³². Such 'release phenomena' include oroalimentary automatisms, bruxism, pedalling activity, wanderings, and emotional responses (ictal fear, sleep terrors)³³. There does also appear to be an unusually high proportion of patients with NFLE reporting a history of parasomnia, up to 34%²⁵. A recent study also found a higher proportion of relatives with parasomnias in relatives of patients with frontal lobe epilepsy compared to relatives of normal control subjects³⁴.

Epilepsy and AEDs may also aggravate OSA. AEDs could reduce respiratory drive and upper airway tone and some drugs are also associated with weight gain. Identification and treatment of both epilepsy and OSA is hence important to optimise patient outcome.

Table 1. Effect of antiepileptic drugs on sleep.

	Effect on sleep						Effects on sleep disorders	
	Sleep efficiency	Sleep latency	Stage I	Stage II	Stage III	REM	Improves/ treats	Worsens
Phenobarbitone			-		0		Sleep onset insomnia	OSA
Phenytoin	0					0 or	None known	None known
Carbamazepine	0	0	0	0	0	0	RLS	RLS
Valproate	-	0			0	0	None known	OSA*
Ethosuximide	-	-		-		-	None known	None known
Gabapentin	0	0	0	0			RLS	OSA*
Lamotrigine	0	0+	0				None known	None known
Topiramate	0		0	0	0	0	OSA*	None known
Tiagabine	-	-	-	-		-	Insomnia	None known
Levetiracetam	-	-	-	-		-	None known	None known
Pregabalin		-	-	-		-	None known	OSA*

0, no change; -, not reported; +, increase; -, reduction; OSA, obstructive sleep apnoea; REM, rapid eye movement; RLS, restless leg syndrome. *Due to change in weight. †Lamotrigine may be associated with insomnia, clinical observation but rarely reported in the literature.

Differential diagnosis of paroxysmal nocturnal events

Paroxysmal nocturnal events often represent a differential diagnostic challenge for the clinician. Patient recall is often poor, and the bed partner is often the person instigating contact with medical professionals. Despite this, there may still be a limited history as events occur during the night when it is dark, and the witness may be asleep at the onset and miss part of the events. The witness may also not be alert enough to provide a good description of the events. However, there may be no witness account at all for individuals who sleep alone. ‘Routine investigations’ such as EEG are often normal and hence not helpful for the differential diagnosis.

There are, however, some clinical features that may help in differentiating nocturnal events:

1. Timing of events during sleep, i.e. soon after sleep onset or later towards morning?
2. How often during the night, i.e. how many events each night?
3. Frequency of events, i.e. do events occur every night, once per week, once per month, less frequently and does the frequency vary over time?
4. Lifetime duration, i.e. at what age did events start and has there been any change in frequency/severity over time?

Frontal lobe epilepsy

1. Can occur throughout night but most likely in transition periods and NREM light sleep
2. May occur several times per night, often in clusters (may be unrecognised)
3. Frequency varies
4. Age at onset variable, often childhood or teens.

Three main types of nocturnal frontal lobe seizures have been described: paroxysmal arousals, nocturnal paroxysmal dystonia and episodic nocturnal wanderings²⁵.

Paroxysmal arousals consist of brief, sudden eye opening, head raising or sitting up in bed, a frightened expression and, sometimes, vocalisation. Nocturnal paroxysmal dystonia involves dystonic posturing and hypermotor (complex motor) phenomena. Episodic nocturnal wanderings are longer in duration (1–3 minutes), with associated stereotyped dystonic movements²⁵. People with nocturnal frontal lobe epilepsy (NFLE) will commonly have more than one of these seizure types. Daytime inter-ictal EEG shows epileptiform abnormalities in up to one-third of cases; this increases to 50% of nocturnal EEGs. Ictal EEG is often unhelpful with no clear changes or only myogenic artefacts. Occasionally there may be subtle features such as electrodecrement or rhythmic frontal slow.

If seizures are very brief, it can be particularly difficult to obtain correct diagnosis. However, distinguishing on the basis of frequency, time of night and stage of sleep can be particularly useful, as mentioned above. Furthermore, there are semiological features that can help distinguish between epilepsy and parasomnia. Importantly, brevity, sitting, standing/walking, preceding arousal or fearful emotional behaviour are not good differentiators. Stereotypy and dystonic posturing are more common features in seizures, while yawning, waxing and waning, prolonged duration (over two minutes) and indistinct offset are more common in parasomnias²⁶. This last feature is quite a notable difference between seizures and NREM parasomnias on video. Derry and co-workers have devised a scoring system (the frontal lobe epilepsy and parasomnia or FLEP scale) and more recently also a diagnostic decision tree to facilitate differentiation of seizures and parasomnia^{26, 27} (Table 2).

Parasomnias

Parasomnias are abnormal events occurring in association with sleep that are classified according to the sleep stage from which they occur. NREM parasomnias occur from deep NREM sleep (stage III) and REM sleep behaviour disorders (RBD) occur during REM sleep.

NREM parasomnia

1. Occur in the first third of the night
2. 1–3 episodes per night
3. Frequency varies
4. Onset in childhood.

NREM are often most difficult to differentiate from nocturnal epileptic seizures. As for nocturnal frontal lobe seizures, there are also three main types of NREM parasomnia: confusional arousal, night terrors (pavor nocturnis) and sleep walking (somnambulism). There are however more uncommon types, such as sleep eating and sleep sex. There is often a family history of NREM parasomnias that can be of any type, not necessarily the same for all affected family members. Symptoms are often exacerbated by sleep deprivation, fever and stress. For some patients alcohol may be a trigger, but this has been disputed²⁸. Other sleep disorders causing sleep deprivation (such as obstructive sleep apnoea and periodic limb movements of sleep) may also exacerbate NREM parasomnias.

Table 2. Frontal lobe epilepsy and parasomnia (FLEP) scale.

Clinical feature		Score
Age at onset		
What age did the patient have their first event?	<55 years	0
	≥55 years	-1
Duration		
What is the duration of a typical event?	<2 min	+1
	2-10 min	0
	>10 min	-2
Clustering		
What is the typical number of events to occur in a single night?	1 or 2	0
	3-5	+1
	>5	+2
Timing		
At what time of night do the events most commonly occur?	Within 30 minutes of sleep onset	+1
	Other times (including if no clear pattern identified)	0
Symptoms		
Are events associated with definite aura?	Yes	+2
	No	0
Does the patient wander outside the bedroom during the events?	Yes	-2
	No (or uncertain)	0
Does the patient perform complex, directed behaviours (e.g. picking up objects, dressing) during event?	Yes	-2
	No (or uncertain)	0
Is there a clear history of prominent dystonic posturing, tonic limb extension or cramping during events?	Yes	+1
	No (or uncertain)	0
Stereotypy		
Are the events stereotyped or variable in nature?	Highly stereotyped	+1
	Some variability/uncertain	0
	Highly variable	-1
Recall		
Does the patient recall the events?	Yes, lucid recall	+1
	No or vague recollection only	0
Vocalisation		
Does the patient speak during the event and if so, is there subsequent recollection of speech?	No	0
	Yes, sounds only or single words	0
	Yes, coherent speech with incomplete or no recall	-2
	Yes, coherent speech with recall	+2
Total score		

Scores: ≤0 very unlikely to have epilepsy; >3 very likely to have epilepsy; +1 to +3 relatively high chance of epilepsy and further investigation would be required in these individuals

Treatment of NREM parasomnias is mainly non-pharmacological, including sleep hygiene and avoiding triggers. Patients can be reassured that the parasomnias themselves are benign but safety aspects (such as ensuring doors and windows are properly closed and locked and that objects with which patients can hurt themselves or partners are locked away) are important to avoid injury to patient or bed partner. In more severe cases pharmacological treatment may be indicated. There are no randomised controlled treatment trials of NREM parasomnias but there are case series reporting efficacy of both long-acting benzodiazepines (clonazepam) and antidepressants (for example paroxetine or clomipramine)^{35,36}.

NREM parasomnias have long been considered a disorder of arousal. This is supported by continued delta activity noted on EEG following arousals. There also appears to be a dissociation between sleep depth and wakefulness in different parts of the brain note both on EEG and during a SPECT study during sleep walking³⁷. Events are often triggered by external stimuli and there may be abnormal arousal responses following arousal. Lately, studies have suggested that people with NREM parasomnias may have dysregulation of slow wave sleep (SWS) regulation and intrinsically abnormal SWS. This is supported by an increased number of arousals even on nights with no events, reduced SWS activity in the first sleep cycle and different time course SWS decay overnight. People with NREM parasomnias may also have atypical response to Sleep deprivation (SD) with increased number of awakenings from SWS after SD and increased frequency and complexity of events after SD³⁸.

REM sleep behaviour disorder (RBD)

1. Occur during second half of night
2. 1–2 episodes per night (but often smaller movements more frequently during REM sleep)
3. Frequency varies (but usually most if not every night)
4. Mean age at onset 50–55 years.

Normally there is muscle atonia during REM sleep to ensure we do not act out our dreams. In REM sleep behaviour disorder (RBD) there is loss of this normal atonia during REM sleep. For a diagnosis of RBD there must also be a history of or observed motor activity during REM sleep. There will often be vivid dreams with some recall, but patients are usually unaware of events. Movements are often reported to be violent and may injure the bed partner. However, during polysomnography, a wide range of movements and behaviours can be seen and it is possible that it is the violent movements that wake the bed partner up and is hence reported. Onset is often later in life and in a large proportion of cases (30–90% depending on study and duration of follow up), RBD is symptomatic of an underlying neurodegenerative disorder such as dementia, Parkinson’s disease, multiple system atrophy or cerebrovascular disease^{39–41}. RBD may pre-date the onset neurodegenerative disorder. It has been suggested that the risk of developing Parkinson’s disease is related to the severity of loss of REM atonia on polysomnography⁴². RBD may also be secondary to withdrawal from alcohol or sedative drugs or precipitated by drugs including tricyclic antidepressants, SSRIs or other types of antidepressants (mirtazapine). It may also be seen in younger patients with other sleep disorders such as narcolepsy. In these patients there does not appear to be any increased risk of developing neurodegenerative disorders and the underlying mechanisms for the RBD may be different.

Treatment includes withdrawal of drugs that may contribute and safety precautions, as for the NREM parasomnias (see above). Even though patients with RBD rarely leave the bed, there is a risk of falling out of bed if movements are violent. Protecting the bed partner is important and sometimes sleeping in separate beds is warranted. RBD often responds well to low doses of clonazepam (0.5–2 mg). Again, there are no randomised controlled trials. More recently, Melatonin has been shown to be an effective treatment of RBD, often in higher doses, up to 12 or even 15 mg⁴³.

Sleep-wake transition disorders

The most common of these are hypnic or myoclonic jerks that occur on going to sleep or waking. The jerks are benign in nature and do not require any treatment apart from reassurance of their harmlessness.

Rhythmic movement disorders are less common sleep wake transition disorders:

1. Occur at wake- sleep transition
2. Many times per night
3. Every night
4. Usually in children or adults with learning disability but can occur in adults of normal intelligence.

Rhythmic movement disorders are characterised by repetitive movements occurring immediately prior to sleep onset and can continue into light sleep. The most dramatic type is head banging (jactatio nocturna) but other movements, such as body rocking, can also be seen. Movements often start in infancy or childhood and persistence of movements beyond the age of ten is often associated with learning disability or autism. Movements can however also continue in adults of normal intelligence. Patients are usually aware of movements. It has been suggested that it might represent a learnt behaviour and it is often difficult to treat. Protection of the patient, i.e. padding of bedhead or a helmet, may be required in severe cases. Benzodiazepines, tricyclic antidepressants or gabapentine can be tried but responses are usually disappointing.

Periodic limb movements of sleep (PLMS)

1. Occur in the early part of the night/throughout
2. Series of > 4 in any sleep stage, up to hundreds per hour
3. Every night
4. Idiopathic form rare under the age of 40 years.

Periodic limb movements of sleep (PLMS) can occur in association with restless leg syndrome (RLS) or separately. Many people with RLS also have PLMS but the converse is not true and most people with PLMS do not have RLS. Periodic limb movements often consist of typical dorsiflexion of toes and ankle but may also affect the knee, hip or arms. Movements are repetitive, occurring every 5–90 seconds. Movements can occur during all stages of sleep, including REM sleep. PLMS may occur in up to 50% of people over 50 years of age and are sometimes associated with daytime movements. The periodic limb movement index (PLMI) averaging the number of movements per hour may be helpful to ascertain severity of symptoms. Less than five per hour is likely to be normal in younger people but this cut-off may be too low a limit in older patients. Movements are only clinically insignificant if associated with daytime symptoms such as excessive daytime sleepiness (periodic limb movement disorder – PLMD).

PLMS can be familial but can also be secondary and associated with iron deficiency, pregnancy, peripheral neuropathy, neurodegenerative diseases and, rarely, spinal cord lesions. Antidepressant drugs (SSRIs and tricyclics), neuroleptics, lithium, caffeine and alcohol may also be associated with PLMS. Patients should have iron and ferritin levels checked and supplements provided if levels are low or within the lower end of the reference interval if Ferritin <50 ug/litre). Treatment may be required if symptoms are severe and there are frequent arousals. In the first instance, any medication contributing to the symptoms should be discontinued if possible. Other treatment options are symptomatic and include dopamine agonists (ropinirole or pramipexole), anticonvulsants (gabapentin, pregabalin, carbamazepine), benzodiazepines (clonazepam) or opiates (tramadol).

Narcolepsy

Narcolepsy is a well-defined chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally, in particular REM sleep. Features of REM sleep intrude into wakefulness and other stages of sleep. Patients with narcolepsy do hence not only have difficulties staying awake but also staying asleep.

There is a classical tetrad of symptoms:

1. Excessive daytime somnolence (EDS)
2. Cataplexy
3. Hypnagogic or hypnopompic hallucinations
4. Sleep paralysis.

Only 10–15% of patients have the full tetrad. EDS, often in combination with sleep paralysis and/or hallucinations, is the presenting symptom in around 90%. The sleepiness is continuous but will intermittently worsen, resulting in an uncontrollable urge to sleep even in inappropriate situations, and often interferes with normal activities. Even a brief nap is often refreshing. Around 60–70% of patients have cataplexy that can develop years after the initial presentation, usually within 3–5 years. Episodes with cataplexy may be mistaken for seizures. Cataplexy is a sudden decrease in voluntary muscle tone (especially jaw, neck and limbs) that is usually precipitated by strong emotions such as laughter, anger or surprise. Usually events are often partial, only involving for example the face, head and neck muscles and manifest as drooping of face muscles, jaw dropping, or head nodding. If severe, limbs may be involved, and patients may fall (complete attack). Consciousness is preserved throughout but if episodes last longer than two minutes, patients may go into REM sleep. Sleep paralysis and hallucinations are not specific for narcolepsy but can occur in other sleep disorders and can also occur in people without sleep disorders, particularly following sleep deprivation. Hypnagogic denotes events associated with sleep onset and hypnopompic events associated with sleep offset. There may also be episodes with automatic behaviour or micro sleeps/sleep attacks that occasionally can be mistaken for epileptic seizures or post ictal behaviour.

Narcolepsy is diagnosed using polysomnography and the multiple sleep latency test (MSLT). There is a strong association with HLA type, suggesting that narcolepsy is an autoimmune disorder. Approximately 90% of patients who have narcolepsy with cataplexy have the HLA allele HLA DQB1*0602. However, this is also frequently found in the general population (around 25%) and is therefore in general not helpful for diagnosis. Genetic factors may also be involved but to date no specific gene for narcolepsy has been identified in humans. Loss of hypocretin (orexin) -producing neurones in the hypothalamus has been shown in patients with narcolepsy with cataplexy and it is likely that narcolepsy is due to hypocretin (orexin) deficiency^{44,45}. Low levels of hypocretin have been shown in patients who have narcolepsy with cataplexy but for patients with narcolepsy without cataplexy, levels are similar to control subjects^{46,47} and in this group of patients, CSF analyses are less helpful for the diagnosis.

Treatment of narcolepsy includes sleep hygiene and planned daytime naps, preferably no longer than 15 minutes. EDS is also treated with stimulants; modafinil or amphetamine derivatives (dexamphetamine or methylphenidate). Recently, Pitolisant, a histamine H3-receptor antagonist/inverse agonist was licensed in the UK for treatment of narcolepsy with and without cataplexy and this might in the future be a treatment option, particularly in patients who do not tolerate the commonly used stimulants or where there are contraindications. Cataplexy and other REM sleep phenomena (sleep paralysis and hallucinations) usually respond well to treatment with antidepressants, for example fluoxetine, clomipramine or venlafaxine. Sodium Oxybate taken in the

evening to consolidate overnight sleep can be an effective treatment of both EDS and cataplexy but due to the high cost (permission needs to be sought from local authorities) the usage in the UK is so far limited.

Summary

There are multiple links between epilepsy and sleep. Sleep and sleep deprivation may influence IED and seizures. Primary sleep disorders such as OSA may worsen epilepsy and treatment of these sleep disorders can lead to improved seizure control. Seizures may interfere with night-time sleep structure and cause EDS. Correctly diagnosing paroxysmal nocturnal events remains a challenge even using video-EEG telemetry. Identification and treatment of both sleep disorders and epilepsy is important for optimal patient care.

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CHAPTER 19

Diagnosis and management of dissociative seizures

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Up to one in five people diagnosed with epilepsy will turn out to have dissociative seizures (DS) - psychologically mediated episodes of altered awareness and/or behaviour that may mimic any type of epilepsy^{1,2}. These patients are typically treated with antiepileptic medication for a number of years before the correct diagnosis is made. During this time they are exposed to significant iatrogenic risks including drug toxicity, teratogenic risk (most patients are young women) and the risk, in approximately 10%, of receiving emergency treatment for 'status'^{3,4}. By the time the correct diagnosis is made many patients and their families have already adapted their lives to chronic disability. For some, a medical 'sick role' seems preferable to a psychiatric one from the start. For the majority, however, years of inappropriate medical interventions will have reinforced the patients' view of themselves as medically disabled. The one factor consistently associated with a better prognosis in this and other functional disorders is a short duration of illness at the time of diagnosis: in other words, prompt diagnosis⁵. How to recognise and treat DS is therefore an important subject for all clinicians working in the field of epilepsy.

Definitions and terminology

A review in 1997 found no less than 15 synonyms for this disorder⁶. Some terms (pseudoseizures, hysterical fits) are clearly pejorative and have been abandoned. Others (non-epileptic seizures, non-epileptic events, non-epileptic attack disorder) define the condition by what it is not and may well be interpreted by the patient as suggesting that 'the doctor doesn't know what's wrong with me'⁷. Furthermore, some of these terms are ambiguous. Non-epileptic seizures (NES), for example, is used by some to describe conditions, both medical and psychiatric, that may be mistaken for epilepsy, while on other occasions NES is used as a form of shorthand for the psychogenic attacks alone. The debate about terminology is likely to continue, but in the meantime ICD 10⁸ does in fact provide a perfectly acceptable and useful label - dissociative convulsions. In recognition of the fact that many patients with this disorder do not actually suffer a 'convulsion', the term *dissociative seizures* is probably better.

Psychiatric disorders that may be mistaken for epilepsy

A list of the medical and psychiatric disorders that may be mistaken for epilepsy is given in Table 1. The clinical features distinguishing epilepsy from paroxysmal cardiological, neurological and other medical disorders are reviewed elsewhere in this section^{9,10}. Syncope is probably the most frequent missed diagnosis in non-specialist settings but by the time patients are referred to specialist epilepsy clinics DS is by far the most important differential diagnosis¹. Indeed, the possibility of DS should be one of the first considerations in a patient with medically intractable seizures.

Table 1. The differential diagnosis of epilepsy.

A. Medical causes of paroxysmal neurological dysfunction

1. Syncope

- vasovagal
- cardiogenic

2. Neurological

- cerebrovascular
- migraine
- vertigo
- cataplexy
- parasomnias
- movement disorders
- startle-induced phenomena

3. Endocrine and metabolic

- hypoglycaemia
- hypocalcaemia
- hereditary fructose intolerance
- pheochromocytoma
- drugs and alcohol

B. Psychiatric disorders

1. Dissociative seizures

2. Psychiatric disorders that may be mistaken for epilepsy

- panic disorder
- psychosis
- attention deficit hyperactivity disorder
- depersonalisation disorder

3. Factitious disorder

Apart from DS a number of psychiatric disorders may occasionally be mistaken for epilepsy and vice versa. The most important example is panic disorder which may be confused with partial seizures that feature anxiety as part of the aura^{11,12}. The cognitive symptoms of panic disorder (specific feared consequences of the attack, such as a fear of choking, having a heart attack, dying, losing control, etc), the presence of environmental precipitants (crowded places, queues in supermarkets, etc) and the avoidance of such situations (agoraphobia) help identify panic. The unusual subjective quality of ‘ictal fear’, abrupt onset without environmental triggers and the presence of other epileptic semiology are useful in recognising the epileptic origin of such symptoms in partial seizures. Very rarely, paroxysmal symptoms in psychosis (hallucinations, thought block) may raise the possibility of epilepsy, and attentional problems in a child may raise the differential diagnosis

of attention deficit hyperactivity disorder and petit mal seizures. An uncomfortable sense of unreality concerning one’s self (depersonalisation) or the environment (derealisation) is not uncommon in temporal lobe seizures. These symptoms may be the primary complaint in depersonalisation disorder and are a non-specific feature of affective disorder and psychosis¹³. In psychiatric disorder these phenomena are usually of relatively gradual onset, prolonged duration and accompanied by other psychiatric symptoms. Overall, the abrupt onset, brief duration and highly stereotyped nature of epileptic symptoms help distinguish them from functional psychiatric disorder.

Factitious disorder and dissociative seizures: the concept of unconscious symptom generation

Factitious disorder (Munchausen’s syndrome) refers to the situation in which a patient is discovered to be (or admits) deliberately feigning symptoms. The most important feature, however, and this is critical for the diagnosis, is that in factitious disorder the patient’s motivation is held to be psychological (understandable in terms of the patient’s psychological background, personality, dependency needs, etc). By contrast *malinger* (not a medical diagnosis) involves fraudulently imitating illness to achieve some obvious practical advantage (e.g. compensation, to avoid a criminal conviction, to obtain social security benefits).

By definition, DS are regarded as being involuntary or unconscious. By consensus, the majority of patients with such seizures are believed to meet this criterion. For some, however, the fact that experienced clinicians judge this to be the case is not persuasive. For sceptics, there are three objective features of DS that are worth considering: 1) the majority of patients are compliant with their antiepileptic drugs (AEDs), often for many years and to the point of toxicity^{4,14}; 2) when patients are admitted for telemetry the majority have a seizure in a setting which they must surely recognise involves intensive monitoring; 3) the seizure is usually a poor imitation of epilepsy. None of these points is by any means conclusive but if deception is involved, it is of a kind that is difficult to understand.

While psychiatric classification systems assume a dichotomy between conscious and unconscious symptom generation (implying factitious or dissociative seizures respectively) the two are best regarded as opposite ends of a continuum. The concept of *self deception*, something which at a trivial level most people can relate to, lies somewhere in the middle and provides a useful paradigm for understanding how subjective experience, and even complex behaviour, is prone to influences that are not always fully conscious, even in healthy individuals. Gesticulation, talking to oneself, and mind-wandering are all examples of common behaviours and experiences that occur, at least to some extent, outside of conscious control – so-called “everyday dissociation”, see below.

Clinical features of dissociative seizures

Prevalence

From prevalence figures for epilepsy and estimates of the proportion of patients referred to tertiary clinics who have DS, Benbadis and Allen² calculated the prevalence of DS to be between two and 33 per 100,000. However, the true prevalence may be far greater. These authors based their calculation on the assumption that most patients with DS would find their way to specialist clinics because their seizures would persist despite AED treatment in primary care. However, it remains entirely possible that some patients with DS have a (placebo) response to their first AED prescription and are never referred on for specialist advice. This possibility is borne out by a recent population-based study that found DS in a fifth of patients with new-onset seizures, the same proportion of DS reported in specialist services¹⁵.

Demographic characteristics

60–75% of patients are female^{3,14,16,17}. Seizures typically begin in the late teens or early 20s, although there is a wide range^{3,14,16}. A UK study found a median delay between seizure onset and diagnosis of three years³, but even longer delays have been reported by others^{18,19}. Patients with lower educational achievement and of lower socioeconomic groups are probably overrepresented, although not in comparison with epilepsy.

Clinical assessment

No single semiological feature distinguishes DS from epileptic seizures or *vice versa*. The most helpful features, as well as some important pitfalls - symptoms that are commonly mistaken as evidence for epilepsy - are listed in Table 2. Epileptic seizures are brief, highly stereotyped, paroxysmal alterations in neurological function that conform to a number of now well-described syndromes. Broadly speaking, it is any variation from this clinical picture - an *atypical sequence of events* - that will raise the suspicion of epilepsy. Despite 30 years of videotelemetry there is no reliable shortcut to making the diagnosis: to recognise DS the clinician must have experience with epilepsy. Some features worth highlighting are the long duration of DS, their tendency to begin gradually, and to show a waxing and waning of motor activity followed by an abrupt recovery, asynchronous movements (including side-to-side head or body movements), eye closure, ictal crying and preserved recall after a period of unresponsiveness²⁰. An episode of motionless unresponsiveness⁷⁷ lasting over five minutes is unlikely to have an organic cause³. Patients with DS commonly report injuries. Friction burns may be characteristic of DS. Bite injuries are reported in DS, especially to the tip of the tongue and lip²¹, but severe scarring is extremely rare. Seizures during sleep are reported just as frequently in DS (around 50%) as in epilepsy⁶⁵.

Table 2. Comparative semiology of dissociative epileptic seizures.

	Dissociative seizures	Epileptic seizures
Duration over two minutes	common	rare
Recall for a period of unresponsiveness	common	very rare
Motor features		
Gradual onset	common	rare
Eyes closed	common	rare
Thrashing, violent movements	common	rare
Side-to-side head movement	common	rare
Pelvic thrusting	occasional	rare
Opisthotonus, 'arc de cercle'	occasional	very rare
Fluctuating course	common	very rare
Automatisms	rare	common
Weeping	occasional	very rare
^a Incontinence	occasional	common
^a Injury		
Biting inside of mouth	occasional	common
Severe tongue biting	very rare	common
^a Stereotyped attacks	common	very rare

^aThree features that are commonly misinterpreted as evidence for epilepsy have been included. Otherwise the table lists clinical features that are useful in distinguishing DS from epileptic seizures. Figures for frequency of these features are approximate: common >30%; occasional 10-30%; rare <10%; very rare <5%. (Adapted from Mellers²⁰)

Studies of the semiology of DS have focused on motor phenomena and the features of epilepsy lacking in DS. Little attention has been paid to subjective symptoms that might be regarded as the psychiatric phenomenology of DS^{78,79}. Patients with DS commonly report a feeling of being cut off from their surroundings at the onset of their seizure and describe a number of symptoms of autonomic arousal^{66,83-85}. These include tachycardia, perspiration, hyperventilation, peripheral paraesthesia, carpopedal spasm and a dry mouth. Patients may not volunteer these symptoms and sometimes a history of hyperventilation will only emerge from an eyewitness account. Such symptoms are reported by approximately 60% of DS patients, compared with around 30% of patients with partial seizures⁶⁶.

Other features of history which support (but do not prove) a diagnosis of DS include an absence of risk factors for epilepsy, a failed response to AEDs and the presence of risk factors for DS (see below). Here again there are pitfalls. Patients with DS commonly report a significant past neurological history²² as well as a family history of epilepsy²³.

It used to be supposed that the majority of patients with DS also suffered from epilepsy. As studies have become more sophisticated, however, estimates of the prevalence of comorbid epilepsy have become ever smaller. Probably no more than 15 or 20% of patients with DS also have epileptic seizures^{3,16,18,24}. A common scenario is that there is a prior diagnosis of epilepsy in the medical history, but careful examination of the notes shows that it was never substantiated by EEG evidence and may well have been a misdiagnosis. A history of multiple (dissociative) seizure types is given by 20% of patients with DS^{16,18}.

Psychiatric comorbidity

Studies of psychiatric diagnoses in patients with DS have reported a broad range of prevalence figures. High rates of depression, anxiety disorder, personality disorder and post-traumatic disorder have been reported¹⁶. Often the presence of such a history will raise suspicion of DS, but high rates of psychiatric disorder are also seen in association with epilepsy, at least in those patients with intractable epileptic seizures, and may not help distinguish the two disorders²⁵⁻²⁷. A history of previous medically unexplained symptoms is very common in DS and an important pointer to the diagnosis¹⁶.

Ictal observation/examination

An opportunity to observe a seizure may provide invaluable information. Whether the patient is responsive to verbal requests should be established. Careful note should be taken of the type and distribution of movements and whether apparent clonic movements are rhythmic and synchronous (as they usually are in epilepsy) or not (DS). Following a generalised tonic-clonic seizure the corneal reflex will usually be absent and plantar responses extensor. Pupils will be unresponsive to light in organic states of impaired consciousness. If the patient's eyes are shut the examiner should attempt to open them noting any resistance (DS). A simple test to look for avoidance of a noxious stimulus is to hold the patient's hand over their face and drop it: in DS the patient may be seen to control their arm movement so their hand falls to one side. If the eyes are open, evidence of visual fixation may be sought in two ways. The first involves rolling the patient onto their side. In patients with DS the eyes will often be deviated to the ground. If this is the case, the patient should be rolled onto the other side to see if the eyes are still directed towards the ground (the 'Henry and Woodruff sign')³¹. A second useful manoeuvre is to hold a small mirror in front of the patient and look for evidence of convergent gaze and fixation on the reflection. This procedure will often stop the seizure. Patients with factitious disorder may learn to produce the 'correct' response (i.e. the one more consistent with epilepsy) in all of these examination procedures.

Investigations

EEG

Unfortunately the EEG still contributes to diagnostic errors in this group of patients. Non-specific EEG abnormalities are found in up to 15% of healthy individuals and all too often interpreted as supporting a diagnosis of epilepsy. Narrowly defined epileptiform abnormalities are much less common, but still encountered in up to 1% of the healthy population^{29,30}. The risk of a 'false positive' EEG is compounded in patients with DS by the fact that both non-specific and epileptiform EEG abnormalities may be more common in patients with DS than in healthy individuals, including those who do *not* have comorbid epilepsy³¹. This is almost certainly because a variety of neurological insults associated with learning difficulties are common in patients with DS and may be associated with EEG abnormalities in the absence of epilepsy. Interestingly, patients with borderline personality disorder (also common in DS) have also been reported to have a high prevalence of non-specific EEG abnormalities³².

VideoEEG telemetry

VideoEEG (vEEG) telemetry is the gold standard investigation. A good quality video which captures the onset and evolution of the seizure will on its own often allow a confident diagnosis. The diagnostic electrographic findings are: for epilepsy, 1) ictal epileptiform discharges; 2) post-ictal slowing; and in DS, 3) an intact alpha rhythm when the patient is demonstrably unresponsive³. Again, there are some traps: in particular, movement artefact may obscure or even be mistaken for epileptiform discharges. There are documented cases of patients having their first ever, and possibly only, DS during telemetry, sometimes as an elaboration of a simple partial seizure³³. This underlines the importance wherever possible of showing the video to an informant to establish that the seizure is representative of the patient's *habitual* attacks. In addition to the cost of vEEG and its restricted availability there are a number of important clinical limitations. The technique is of limited use in a patient who has infrequent seizures. Care must be taken in patients who have multiple seizure types to ensure that an example of each seizure is seen.

Special mention should be made of simple partial seizures and frontal lobe seizures which are often not accompanied by any electrographic changes on the ictal scalp EEG^{34,35}. Frontal lobe seizures in particular may have bizarre behavioural features which are now well known to specialists but may easily be mistaken for DS³⁶. The highly stereotyped nature and very brief duration of the seizures are helpful features on video. If seizures occur in sleep, as they often do in frontal lobe epilepsy, the EEG will be helpful, demonstrating seizure onset during electrographically documented sleep. In DS by contrast (around 50% of patients with DS report seizures arising from sleep)⁶⁵ the EEG will reveal that the patient wakes and then has their seizure³⁷.

A number of studies have demonstrated that placebo methods such as intravenous injection of saline can be used to provoke a seizure in up to 90% of patients with DS³⁸. Clearly these studies raise ethical concerns related to the use of placebo. Most recently, however, McGonigal and colleagues have combined simple suggestion with routine photic and hyperventilation stimuli, fully disclosing the aims of the procedure to patients³⁹. A total of 60% of patients had a DS provoked in this way compared with 33% in a control group who received identical activation procedures but without suggestion. These authors estimate they were able to reduce the need for prolonged telemetry admission in 47% of patients. Provocation may be of particular value in patients who have infrequent seizures and would otherwise be unsuitable for telemetry. There is a small risk of false positive results with this technique (provoking a DS in a patient with epilepsy) and it is therefore critical that an informant who has witnessed the patient's seizures is available to confirm that the provoked seizure resembles their habitual seizures.

Ambulatory EEG monitoring and video recordings obtained by patients' carers may be very helpful

with the accepted and obvious limitations of lacking video correlation in the first and usually failing to capture seizure onset in the second⁴⁰.

Serum prolactin

Serum prolactin rises after tonic-clonic epileptic seizures, peaking between 20 and 30 minutes following the seizure⁴¹. The post-ictal prolactin level should be compared with a baseline measure taken at approximately the same time of day. A prolactin rise is less reliable following complex partial seizures, may be absent following serial epileptic seizures or in status epilepticus, and is not seen following simple partial seizures. False positive rises are now known to occur following syncope⁴² and, more significantly, DS⁴³ and the test is falling out of favour. However, a negative finding after an apparent tonic-clonic seizure may still be very helpful. A recent study has reported higher creatine kinase levels in patients with tonic-clonic status compared with DS status but again there were false positives and negatives⁶⁷.

Psychiatric formulation: an aetiological model of DS

By analogy with epileptic seizures, which are a symptom of paroxysmal neurophysiological abnormality that may have many causes, a useful model of DS would attempt to account for the mechanisms underlying individual seizures as well as for background predisposing factors. As yet there is no widely agreed model. However, many putative risk factors for DS have now been reported and studies seeking to clarify the psychiatric phenomenology and the neurophysiology of dissociative states are ongoing.

Dissociation

For practical purposes, dissociation may be defined as a psychologically mediated alteration of awareness and/or control of neurological function. Some have argued for more specific uses of the term⁴⁴ but defined in this way dissociation encompasses a spectrum of mental processes including normal phenomena, such as focused or divided attention (e.g. 'domestic deafness', mental absorption), and pathological states involving perceptual, cognitive and motor function. The advantage of such a definition is that, by explicitly assuming (and it is an assumption) that dissociative disorders lie on a continuum with normal experience, it facilitates an empathic understanding of what might otherwise seem unintelligible, if not frankly unbelievable, behaviour. This is equally important for professionals, patients and carers.

The psychophysiological basis for dissociative states is not understood. Many patients with DS describe becoming gradually cut off or distant from their environment and experience symptoms of autonomic arousal during their seizures. This suggests that for some patients, DS may represent a dissociative response to paroxysmal physiological arousal triggered by intense emotion. Some patients may even be aware of 'giving in' to a trance-like state to escape from distressing emotions⁸⁰. Most patients, however, deny emotional symptoms in their attack (DS may be likened to 'panic attacks without panic')⁶⁶, the hypothesis being that the triggering emotion is concealed by the dissociative state (for Freud this was the primary gain of "hysterical" symptoms). However, clinical experience suggests that a proportion of patients who initially deny triggers for their attacks are eventually able to recognise highly specific and emotive cues (for example related to traumatic past experiences). Clearly, this model of dissociative mechanisms gives rise to a number of testable hypotheses which require further research.

Predisposing, precipitating and maintaining factors

Studies of psychosocial correlates of DS have revealed a number of potential predisposing, precipitating and maintaining factors which are summarised in Table 3. Adverse or traumatic experiences, particularly in childhood, are a common underlying theme. Sexual, physical and emotional abuse are well replicated associations^{45-47,68} but other traumatic experiences or situations

that foster enduring low self-esteem, for example being bullied at school or unrecognised learning difficulties, may be over-represented⁴⁸. The high prevalence of abnormal personality in DS^{49,50} may be an effect of adverse experiences at a stage of development when personality attributes are formed. None of these features, however, is unique to patients with DS; they are seen in patients with other psychiatric disorders, including somatoform presentations other than DS^{47,51}. Why some children exposed to grossly abnormal experiences develop psychiatric disorder later in life, but others do not, and what determines the form the illness takes, is not understood. Further studies of coping styles, putative dissociative and somatising traits, and how these are related to childhood traumatic experiences will help tease apart the undoubtedly complex individual/environmental interactions involved.

Table 3. Predisposing, precipitating and maintaining factors in dissociative seizures.

	Psychological	Social
Predisposing	Perception of childhood experience as adverse	Adverse (abusive) experiences in childhood
	Somatising trait	Poor family functioning
	Dissociative trait	Traumatic experiences in adulthood
	Avoidant coping style	Modelling of attacks on others with epilepsy
	Personality disorder	
	Mood disorder	
Precipitating	Perception of life events as negative/unexpected	Adverse life events
	Acute panic attack/syncope	
Maintaining	Perception of symptoms as being outwith personal control/due to disease	Angry/confused/anxious reaction of carers
	Agoraphobia: avoidant and safety behaviour	Fear of responsibilities of being well/benefits of being ill
	Angry/confused/anxious reaction to diagnosis	

There is no evidence at present for biological factors which are therefore not listed in the table. However, there may be genetic influences on relevant personality attributes, coping styles and traits. (Adapted from Binzer *et al*⁴⁵)

One study has presented evidence of adverse events in the year prior to onset of DS which might be regarded as precipitating factors for the disorder⁴⁵. Once the disorder is established a number of maintaining factors may operate. Agoraphobic avoidance is more common in patients with DS than in epilepsy and serves to heighten anxiety about having seizures which in turn makes seizures more likely⁶⁶. Anxiety about the seizures will also be fuelled by conflicting diagnoses and advice received from the numerous contacts patients have with doctors, paramedics, accident and emergency staff as well as friends, support groups and the internet. Finally, for some individuals at least, the benefits of the sick role may provide an acceptable alternative to the responsibilities of healthy life⁵², and carers, unwittingly or otherwise, may play an important role in perpetuating disability. The stigma attached to mental illness undoubtedly has an important role in shaping the medical presentation of somatoform disorders and contributes to the reluctance many patients have in accepting psychiatric treatment.

Management

An approach to discussing the diagnosis with patients

The way in which the diagnosis of DS is presented to the patient is possibly the single most important factor determining outcome (Table 4). A clear explanation of the reasons for concluding the patient does not have epilepsy should cover both clinical features and investigation findings. It is important that patients are not left with the impression that investigations alone hold the key to diagnosis; a quest for further tests might otherwise ensue. Once the patient understands that epilepsy and other 'medical' causes have been excluded they will often be extremely sensitive about being accused of putting on their attacks. The clinician should put aside any prejudices they may have in this respect, suspend disbelief if necessary, and reassure the patient that their attacks are real, disabling and involuntary.

Next, an intelligible explanation of what the patient does have is required. The concept of dissociation can be explained as involuntary episodes of 'switching off' or going into a 'trance'. Examples of selective attention (mental absorption - not hearing one's name called when reading) and divided attention (travelling home from work and remembering nothing of the journey) can be used to illustrate the involuntary, unconscious nature of dissociative phenomena and how we can all be unaware, or have no memory of, sensory experience or complex activities despite perfectly normal neurological function.

Table 4. Presenting the diagnosis of dissociative seizures.

The discussion should cover:

1. *Explanation* of the diagnosis

- Reasons for concluding they don't have epilepsy
- What they do have (describe dissociation)

2. *Reassurance*

- They are *not* suspected of 'putting on' the attacks
- The disorder is very common

3. *Causes* of the disorder

- Triggering 'stresses' may not be immediately apparent
- Relevance of aetiological factors in their case
- Maintaining factors

4. *Treatment*

- DS may improve simply following correct diagnosis
- Caution that AED withdrawal should be gradual
- Describe psychological treatment

Patients often express a fear that they are 'mad' and are reassured to hear how common the problem is and that it is treatable. In trying to answer the question 'what causes the seizures?' a helpful approach is to describe the known demographic and aetiological factors as they apply

to that individual, together with a speculative model of how this might be related to dissociation. For example, one might explain: 'We don't fully understand what causes this disorder but two-thirds of people with it have suffered the sort of traumatic experiences you have described. We can't explain the link for certain, but it may be that when people are exposed to repeated frightening incidents as a child they learn to switch off. Initially this is a helpful thing for them to do, it protects them emotionally at the time. But it may come back later in life as these seizures.' It is important not to suggest abuse as a possible aetiological factor if this history has not emerged spontaneously for fear of encouraging 'false memories'.

A description of maintaining factors is especially useful when other aetiological factors are not apparent. Patients will often recognise that their confusion about the nature of the seizures, avoidance of situations in which they fear having one, and the protective reactions of carers together create a 'vicious circle' whereby fear of having attacks may eventually become the most important 'cause' of them. A few patients clearly identify stress as a trigger for individual attacks, but most do not. This can be a very difficult issue. It may be helpful to explain that many patients are initially unable to identify triggers for their attacks but that these often become apparent with treatment. Further, that when triggers are found they often turn out to be fleeting stressful or unpleasant thoughts that the patient was barely aware of (or could not easily remember) that have little to do with their immediate circumstances. It may be useful to explain that we all think at many different levels at any one time and some of what we are thinking about is instantly forgotten. By way of illustration, asked to introspect for a moment, most patients will acknowledge that they have been thinking of other things while listening to the doctor's explanations. Examples of the link between physical symptoms and emotional state, and of the complex automatic behavioural accompaniments to emotions (as seen with grief or with rage) may help illustrate some of the physical attributes of seizures.

Finally, in describing treatment and prognosis it is worthwhile emphasising that simply understanding the nature of the problem and withdrawing AEDs is all that is required for some patients⁵³. For those who have DS alone the news that they may come off antiepileptic medication is usually very welcome. It is important, however, to caution against abrupt withdrawal. Guidelines for AED withdrawal have been published by Oto and colleagues⁷⁰.

Information about DS is available online through two comprehensive and carefully devised websites written by neurologists for patients.

The first of these, www.neurosymptoms.org also covers functional neurological symptoms in general. The second, www.nonepilepticattacks.info includes specific self-help guidance for people with DS. Both are extremely useful resources.

Patients who have comorbid epilepsy often pose the most difficult management problems. Where both types of seizures are ongoing the main challenge will be to clearly identify, with the patient and carers, the different seizure types: residual uncertainty may undermine psychological treatment and lead to over-medication in order to 'play safe'. Showing patients and carers videos of seizures captured in telemetry is useful but the semiology frequently changes, and the issue often requires regular review. In this situation home videos of seizures may help to avoid repeating vEEG telemetry.

Treatment

The paroxysmal nature of DS, prominent somatic symptoms of arousal in many patients and an association with agoraphobic avoidant behaviour suggest that techniques developed in cognitive behavioural therapy (CBT) for the treatment of panic disorder might readily be adapted for

DS^{59,62}. A number of uncontrolled studies have now shown that CBT is associated with significant improvement^{63,73,74}. More recently, a randomised controlled trial has demonstrated a significant advantage of CBT compared with standard outpatient care⁷⁵. Patients receiving CBT were three times more likely to become seizure free by the end of treatment. However, improvement was seen in both CBT and standard treatment groups and by six months follow-up the difference in outcome was no longer statistically significant. A second small randomised controlled trial has also suggested the effectiveness of CBT in DS⁸¹. Controlled studies of longer-term outcome following treatment are required, as are comparisons of different treatment approaches, including evaluations of brief simplified treatments which might be delivered more easily outside specialist neuropsychiatry services. Techniques developed for post-traumatic stress disorder and dysfunctional personality traits may also be helpful, but these and other techniques also require evaluation^{59,64}.

A significant proportion (see below) of patients continue to have seizures despite intensive treatment. A pragmatic approach in such cases is to offer long term-follow up to provide support for the patient and their family, social interventions to improve quality of life, and also to limit the cost and morbidity associated with further unnecessary investigations and medical interventions.

A review of outcome studies⁵ found that after a mean follow-up period of three years approximately two-thirds of patients continued to have DS, and more than half remained dependent on social security. Psychiatric treatment has been associated with a positive outcome in some studies, but not others. A poor prognosis is predicted by a long delay in diagnosis and the presence of psychiatric comorbidity, including personality disorder. Being unemployed and in receipt of disability benefits has recently been reported to be a predictor of poor outcome⁷⁶.

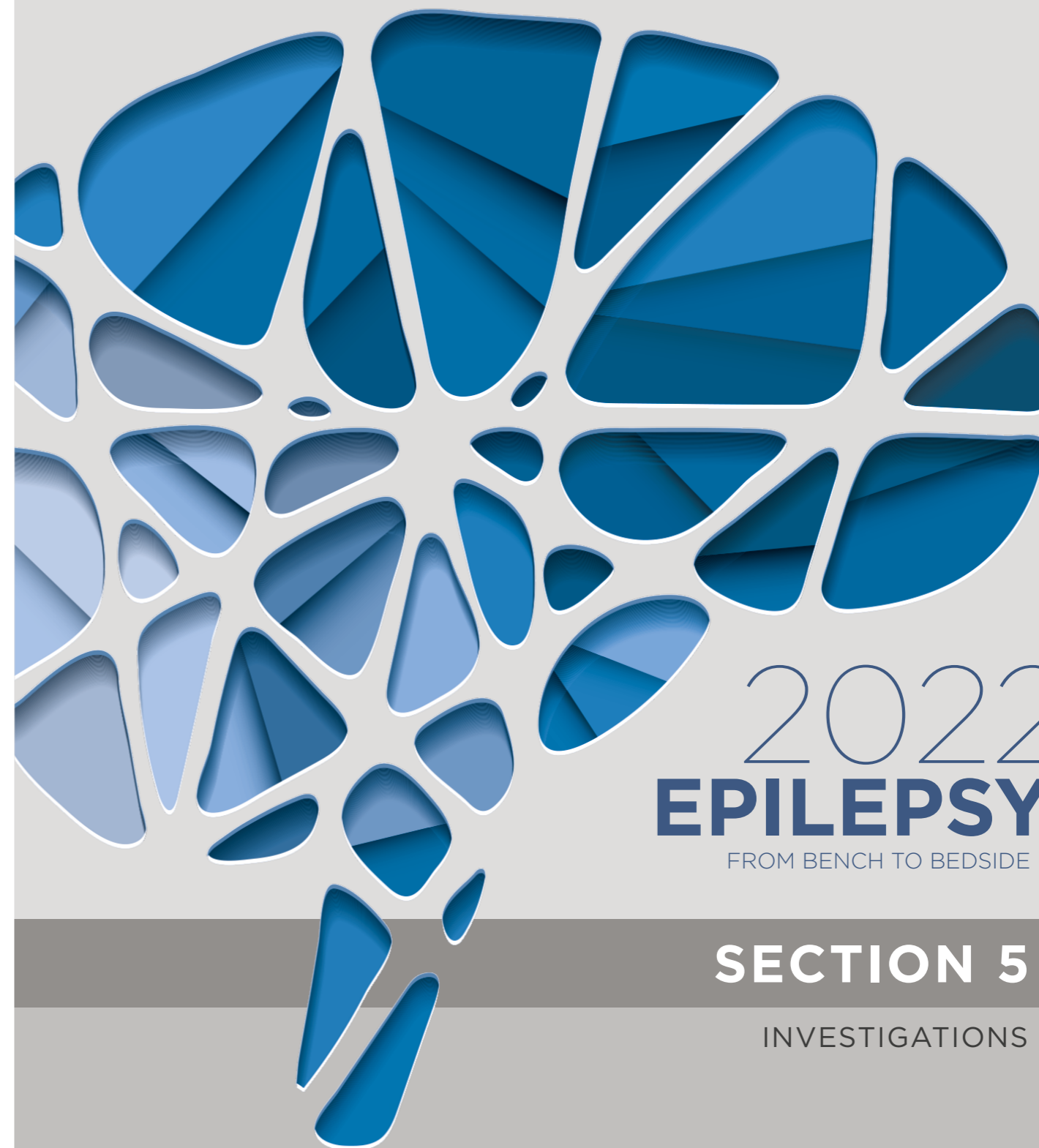
In the UK, a multicentre RCT comparing the effectiveness of standardised medical care with and without CBT⁸² (the CODES trial, www.codestrial.org) has recently been completed. At the time of writing the results are not yet available, but given that this is by far the largest RCT yet conducted in this area, it is likely to guide clinical practice in the future and interested clinicians are encouraged to seek out the published results once they become available.

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 5
INVESTIGATIONS

CHAPTER 20

Neurophysiological investigation of epilepsySHELAGH J.M. SMITH¹ AND ROBIN P. KENNETT². UPDATED 2017 BY TEJAL N MITCHELL³¹National Hospital for Neurology and Neurosurgery, Queen Square, London, and Epilepsy Society, Chalfont St Peter, Buckinghamshire; ²John Radcliffe Hospital, Oxford and ³Addenbrookes Hospital, Cambridge**Routine EEG recording**

Since its discovery in the late 1920s, the electroencephalogram (EEG) has developed into an array of digitally-based techniques, integrated with video and other investigative modalities that retain a central role in diagnosis and management of patients with seizure disorders. In contrast to the technological advances, relatively little progress has been made in understanding the cerebral generators of EEG signals, in part because of their anatomical complexity. Much of what appears on scalp EEG recordings represents the summation of synchronised excitatory or inhibitory post-synaptic potentials in apical dendrites of neurones in superficial neocortex, while deep generators may produce little or no change at the surface.

EEG is not always used appropriately in epilepsy care; evidence-based guidance on its role is limited by a paucity of high quality data and methodological deficiencies in published studies¹. Furthermore, the limitations of scalp EEG may not be fully appreciated by non-specialists, and EEGs can be misinterpreted if there is insufficient knowledge of the range of normal and non-specific phenomena – this being a common reason for over-diagnosis of epilepsy².

In general, sensitivity of routine inter-ictal EEG for detecting epilepsy and its specificity for distinguishing epilepsy from other paroxysmal disorders are both limited. Published figures for diagnostic sensitivity of EEG range between 25 and 55%; up to about half of patients with epileptic disorders may have one normal inter-ictal EEG, and around 10% of patients with epilepsy never show epileptiform discharges³. Hence, a normal or negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure.

Importantly, demonstration of epileptiform abnormalities in the EEG does not in itself equate to epilepsy or indicate that the patient has a seizure disorder. Non-epileptic individuals show epileptiform abnormalities in the EEG in a number of circumstances. A large study of standard EEGs in healthy mostly male adults with no declared history of seizures showed epileptiform discharge in 0.5% of the subjects⁴. A slightly higher incidence of 2-4% is found in healthy children and in non-epileptic patients seen in hospital EEG clinics. The incidence rises substantially to 10-30% in patients with cerebral pathologies such as tumours, previous head injury, cranial surgery or congenital brain injury⁵, and patients with pure psychogenic type non-epileptic seizures have a higher incidence of epileptiform EEGs than normal subjects⁶. Thus, great caution is necessary when assessing the significance of epileptiform activity in such circumstances, particularly if the history offers little or no indication that the patient has epilepsy on clinical grounds.

1. *An EEG should be performed to support a diagnosis of epilepsy in patients in whom the clinical history suggests that the event was likely to be epileptic*
2. *EEG cannot be used to exclude a diagnosis of epilepsy in a patient in whom the clinical history suggests an event of non-epileptic origin*
3. *The EEG cannot and should not be used in isolation to make a diagnosis of epilepsy*

(Adapted from NICE guidelines¹)

Epileptiform phenomena

EEG features classified as epileptiform are spike discharges, spike or polyspike wave complexes, and sharp waves. Some types of epileptiform phenomena are strongly correlated with clinical epilepsy; others are weakly linked to active epilepsy, or have limited association with seizure disorders. Three per second spike-wave discharge in childhood absence epilepsy and the hypsarrhythmic pattern of West syndrome are examples of epileptiform phenomena that are closely correlated with an epileptic disorder. The EEG of normal subjects can show a range of spiky features, particularly during sleep. Physiological and pathological but non-epileptogenic variants include wicket spikes, 14 and 6 Hz spikes, rhythmic mid-temporal theta, and sub-clinical rhythmic epileptiform discharge in adults (SREDA). Mostly, these are not associated with epilepsy, but non-epileptogenic variants are a potential source of confusion and EEG misinterpretation.

Diagnostic yield

A number of factors influence whether patients with epilepsy will show inter-ictal epileptiform discharge (ED) in a routine EEG. Children do so more often than older subjects, and certain epilepsy syndromes or seizure types are more likely to show ED. The location of an epileptogenic region is relevant: a majority of patients with temporal lobe epilepsy show ED, whereas epileptic foci in mesial or basal cortical regions remote from scalp electrodes are less likely to demonstrate spikes, unless additional recording electrodes are used. Patients with frequent (one per month) seizures are more likely to have ED than those with rare (one per year) attacks⁷. The timing of EEG recording may be important: investigation within 24 hours of a seizure revealed ED in 51%, compared with 34% who had later EEG⁸. Some patients show discharges mainly during sleep, or there may be circadian variation as in the idiopathic generalised epilepsies.

A routine EEG recording typically takes 20-30 minutes, and should include standard activation procedures of hyperventilation (up to three minutes) and photic stimulation, using published protocols⁹, or specific triggers in rare types of reflex epilepsies (reading and musicogenic epilepsy etc). It is good practice to warn patients of the small risk of seizure induction and obtain consent to activation procedures. Breath counting is a reliable and effective means to test transient cognitive impairment during generalised spike-wave discharges induced by hyperventilation¹⁰. Most centres use the international 10-20 system of scalp electrode placement, but additional electrodes are often useful, especially those that record from the anterior temporal lobe region (superficial sphenoidal electrodes). The yield of routine EEG can be increased by repeat recordings (up to a total of four in adults), or by use of sleep studies, achieved by recording natural sleep or through use of hypnotics to induce sleep. The combination of wake and sleep records gives a yield of 80% in patients with clinically confirmed epilepsy. Whether sleep deprivation is of additional value for

induction of ED is difficult to determine from reported studies, though there is some evidence that it specifically activates ED in idiopathic generalised epilepsies¹¹. An evaluation of different EEG protocols in young people (<35 years) with possible epilepsy found that sleep-deprived EEG (SD-EEG) provided significantly better yield of than routine EEG or drug-induced sleep EEG, and the authors suggested that SD-EEG is the most cost-effective protocol for investigation of new epilepsy¹².

Prolonged inter-ictal sampling using long-term monitoring also increases yield by about 20%, and is now widely available through 24-hour ambulatory multi-channel digital EEG recording.

What are the roles of EEG in diagnosis of epilepsy?

EEG is performed in patients with possible or known seizure disorders to assist accurate diagnosis and provide information about epilepsy type. EEG findings contribute to the multi-axial diagnosis of epilepsy, by establishing whether the seizure disorder is focal or generalised or part of a specific epilepsy syndrome. In a newly presenting case of suspected epilepsy, the physician will ask:

- Does the patient have a focal or generalised seizure disorder?
- Is there evidence of photosensitivity, if the subject is likely to have genetic generalised epilepsy (previously termed idiopathic generalised epilepsy)?
- Are there EEG features indicative of an epileptic syndrome?

Although conceptual division of focal and generalised seizures/epilepsy types is fundamental in epilepsy characterisation, there is overlap in both clinical and electrographic manifestations of focal and generalised seizure disorders. Rapid propagation or generalisation of epileptiform activity related to a structural or metabolic focus can mimic a generalised epilepsy¹³; localised discharges and regional accentuation of generalised spike-wave discharge are widely recognised in genetic generalised epileptic syndromes¹⁴. In some individuals, there may be co-existence of a focal and a generalised seizure disorder¹⁵. In most instances, the clinician will be reasonably certain about seizure type, based on accounts provided by the patient and witness, but when the history is not clear – as with an un-witnessed ‘blackout’ or brief impairment of awareness, EEG can help to distinguish between a focal seizure with focal ED, and an absence type seizure with generalised ED.

Syndromic findings

Relatively specific EEG abnormalities are found in certain epilepsy syndromes, many of which present in childhood or adolescence. In some individuals, the true epilepsy syndrome may not be apparent at initial assessment, necessitating regular electro-clinical appraisal. For example, juvenile myoclonic epilepsy would be the likely diagnosis in an intellectually normal teenager presenting with myoclonic jerks; if that patient went on to develop refractory epilepsy and cognitive decline, the syndromic diagnosis would be revised to a progressive myoclonus epilepsy.

Epilepsy syndromes presenting in neonatal periods and infancy include self-limited neonatal seizures (previously termed benign idiopathic neonatal seizures), in which the EEG shows trace pointu alternans in 75%; early myoclonic encephalopathy and early infantile epileptic encephalopathy (Ohtahara syndrome) with burst suppression in the EEG; West syndrome in which infantile spasms are associated with hypsarrhythmia; and Dravet syndrome (previously known as severe myoclonic epilepsy of infancy) in which generalised spike-wave and photosensitivity are reported.

Genetic generalised epilepsies (previously idiopathic generalised epilepsies)

EEG features in genetic generalised epilepsies comprise generalised spike or polyspike and slow wave discharges at 3–5 Hz, normal background cortical rhythms, and a relatively high occurrence of photosensitivity¹⁶. In *childhood absence epilepsy (CAE)*, the characteristic finding is bilateral synchronous 3 Hz spike-wave, usually lasting between 5 and 10 seconds, and accompanying typical absence seizures. The discharge is often slightly faster than 3 Hz at onset, and tends to slow down towards the end of the seizure. Inter-ictal EEG is normal, but may show runs of occipital rhythmic delta (15–40% of cases), which can persist in some children after remission of absences. Photosensitivity is uncommon (less than 10%), and may be a marker of poorer prognosis, as do myoclonic jerks of the eyes, mouth or limbs. Video recordings now made routinely during standard EEGs help define these variations in CAE, and it is increasingly recognised in paediatric practice that the more precisely the epilepsy syndrome can be defined the more accurate the advice on prognosis and treatment becomes¹⁹. Patients with *juvenile absence epilepsy* are more likely to show polyspike discharge or spike-wave frequency above 3 Hz, and occipital rhythmic delta is not seen. In *juvenile myoclonic epilepsy*, the inter-ictal and ictal EEG characteristic is brief bursts of polyspike (but sometimes single spike) and wave discharge. Photosensitivity is relatively common in JME (40–50%), and seizures can be induced by other reflex mechanisms including reading or praxis induction. Prominent polyspike wave discharge is also seen in *epilepsies with eyelid myoclonia*.

A retrospective evaluation of EEG features in IGE found only one-third showed typical features on the first EEG¹⁷. While serial EEG records were necessary to elucidate syndromic diagnosis, appropriate treatment could be initiated in a majority of cases on clinical grounds at presentation. Absence epilepsy was the syndrome most likely to show diagnostic EEG abnormalities at initial investigation.

Genetic generalised epilepsies beginning in adult life is now an established entity¹⁸. Most cases have either generalised tonic-clonic seizures with or without myoclonus, and electro-clinical manifestations are similar to those epilepsies presenting at earlier ages.

Photosensitive epilepsy. Photosensitivity occurs in about 5% of all epilepsies, usually genetic generalised epilepsies, but also in progressive myoclonus epilepsies. Photosensitivity has age-related expression, with three-quarters of cases having the first photic induced fit between the ages of 8–20 years²⁰, and photosensitivity is twice as common in females. Longitudinal follow-up studies have revealed persistence of photoparoxysmal responses and hence seizure risk in the majority of cases of photosensitive epilepsy, without age limit. Photoparoxysmal EEG abnormalities can occur as an acute symptomatic phenomenon on abrupt withdrawal of alcohol or certain drugs, but are not then associated with long-term risk of epilepsy.

Self-limited childhood epilepsy syndromes. In childhood epilepsy with centro-temporal spikes (previously known as benign childhood epilepsy with centrotemporal spikes or Rolandic epilepsy), the EEG hallmark is focal sharp wave discharges in central and temporal regions, either bilateral or unilateral, and potentiated by sleep. Occasional patients show focal discharges in other brain regions or generalised spike-wave activity. Background cerebral rhythms are normal. Inter-ictal EEGs can show large amounts of ED, although frequent epileptic seizures occur in only around one-quarter of cases, and the EEG trait may manifest without clinical expression. Childhood occipital epilepsy (Gastaut type) has more variable EEG features; paroxysms of occipital spike-wave on eye closure (fixation off sensitivity) are characteristic of the early onset form or Panayiotopoulos syndrome. Otherwise, multifocal discharges, rolandic spikes and generalised spike-wave are common, and the finding of frequent multifocal discharges in a routine EEG should alert one to childhood occipital epilepsy in a child who has occasional seizures or paroxysmal autonomic symptoms.

Landau-Kleffner syndrome (acquired aphasia and epilepsy) and epileptic encephalopathy with continuous spike-and-wave in sleep. These disorders, which may be related, are characterised by continuous slow spike-wave discharge occupying 85% or more of the sleep record. The wake EEG shows variable findings.

Progressive myoclonus epilepsies (PME). The individual disorders which manifest as PME share neurophysiological features – generalised spike-wave discharge, photo-sensitivity, ‘giant’ SEPs, facilitation of MEPs by afferent stimulation, and abnormalities of background cerebral activity, typically an excess of slow activity. The background abnormalities are usually progressive, with marked changes occurring in syndromes with dementia or significant cognitive decline, such as Lafora body disease. Relatively specific findings include vertex sharp waves in sialidosis, occipital spikes in Lafora body, and giant VEPs in Batten’s disease (late infantile neurolipofuscinosis).

Focal epilepsy syndromes. *Mesial temporal lobe epilepsy* with unilateral hippocampal sclerosis²¹ shows anterior/mid temporal inter-ictal spikes, which are ipsilateral or predominant over the pathological temporal lobe in 60% of cases, and a typical rhythmic 5–7 Hz ictal discharge accompanying seizures in 80%. There may also be post-ictal ipsilateral slow activity and potentiation of spikes, both of which are reliable lateralising findings.

Several familial focal epilepsies have now been described. There is variation in phenotypic and EEG expression between families; overall, familial focal seizure disorders tend to be more benign than lesional partial epilepsy. In familial temporal lobe epilepsy, focal temporal spikes are seen in only around 20% of clinically affected cases. EEG findings are a defining feature of familial focal epilepsy with variable foci, which manifests as temporal and extratemporal seizures; the EEG focus is usually congruent with seizure type in individual cases. In autosomal dominant nocturnal frontal lobe epilepsy, inter-ictal EEG is often normal, although rare frontal or fronto-temporal sharp waves or spikes may be present often only in sleep. The ictal EEG is unhelpful or non-localising.

Routine inter-ictal EEG and management of epilepsy

An important question for a patient presenting with a first unprovoked epileptic seizure is risk of seizure recurrence. Here EEG is helpful, since risk is higher when the initial EEG shows unequivocal ED. If so, treatment should be offered after the first tonic-clonic seizure. In a systematic review²², the pooled risk of recurrence at two years was 27% if the EEG was normal, 37% if there was non-specific abnormality, and 58% if epileptiform activity was present. The inherent risk of recurrent seizures is also dependent on the cause of the first attack and declines with time: probably because of these factors, the EEG is more likely to show abnormality if recorded within 48 hours of the seizure⁸.

Inter-ictal EEG does not provide a reliable index of severity or control in seizure disorders. Reduction in the amount of epileptiform activity shows only a weak association with reduced seizure frequency, and antiepileptic drugs (AEDs) have either little or variable effect on discharge frequency. Hence routine EEG has limited value for assessment of treatment effect, except IGE when persistent epileptiform activity or a photoparoxysmal response usually indicates sub-optimal therapy in patients taking sodium valproate or lamotrigine. In general, ‘treating the EEG’, i.e. to abolish spikes, is unnecessary, although there is emerging evidence that suppression of inter-ictal discharges which cause transient cognitive impairment can improve school performance in some children.

A common reason for EEG referral is prediction of likelihood of seizure relapse in the patient who has been seizure free for a number of years and wishes to come off medication. However, the usefulness of EEG recording is uncertain. Relative risk of relapse if the EEG is abnormal ranges

from 0.8 to 6.47 in published studies²³. Some of these studies include both children and adults, or a range of seizure types and epilepsy syndromes, and it is not clear which aspects of EEG may be important – viz demonstration of non-specific abnormality versus ED, prior or persisting abnormality, or *de novo* appearance of ED during the course of or following drug withdrawal. Overall, EEG appears to be more helpful in prediction of seizure relapse in children, and otherwise for identification of epilepsies that carry relatively high risk of relapse, such as photosensitive epilepsy, juvenile myoclonic epilepsy or symptomatic seizure disorders.

Cognitive deterioration. Confusional states or acute/sub-acute cognitive decline in epilepsy might be the result of a marked increase in ED; frequent subtle/clinically unrecognised seizures; a metabolic or toxic encephalopathy; or non-convulsive status. EEG plays an important role in differentiating these causes. However, electrographic confirmation of acute encephalopathy or non-convulsive status in severe symptomatic epilepsies can be very challenging, because these disorders often show substantial overlap of inter-ictal and ictal EEG patterns.

Chronic cognitive decline in epilepsy may be due to a progressive neurological condition underlying the seizure disorder, or an independent neurodegenerative process. EEG demonstration of deterioration in background cortical activity can help to identify an organic brain syndrome, but is unlikely to discriminate as to cause. ‘Epileptic encephalopathies’ notably in childhood seizure syndromes, conceptualise that electrographic epileptiform abnormalities themselves directly lead to cognitive and behavioural impairments above that expected from the underlying aetiology, and that suppression of epileptic activity may minimise such additional impairments.

Long-term EEG monitoring

Long-term monitoring (LTM) in epilepsy is available in all age groups from neonates to the elderly²⁴⁻⁶, and applicable in hospital and community settings. There is now substantial evidence that LTM has a crucial role in the assessment of seizure disorders, as indicated by a recent ILAE Commission report²⁷.

The clinical applications of EEG monitoring are:

- Differential diagnosis of paroxysmal neurological attacks
- Differentiation between nocturnal epilepsy and parasomnias
- Diagnosis of psychogenic non-epileptic seizures
- Characterisation of seizure type and the electro-clinical correlates of epileptic seizures
- Quantification of ED or seizure frequency
- Evaluation of candidates for epilepsy surgery
- Identification of sleep-related epileptiform discharge/electrical status in children
- Electro-clinical characterisation of neonatal seizures
- Monitoring of status epilepticus (convulsive, non-convulsive, electrographic).

LTM methods comprise ambulatory and video-EEG telemetry. Ambulatory EEG is more suited to clinical problems which do not require concurrent synchronised video to document clinical features (though it can be combined with hand-held camcorder), or for monitoring in an outpatient setting or specific environment. In-patient video EEG telemetry is expensive and labour intensive, and often a limited resource. Specialised telemetry units have the advantage of ward-based staff, experienced in identification of subtle clinical events and able to care for patients during seizures. Methods to increase the likelihood of paroxysmal events include reduction in dose of anti-epileptic medication or sleep deprivation. Provocation techniques, such as saline injections, are not recommended as they can result in false positives, and there are ethical issues if the patient is deliberately misled.

Optimal duration of LTM study depends on the clinical problem, and frequency of attacks. Patients are unlikely to benefit from monitoring if paroxysmal events occur less than once per week. Duration of outpatient LTM is to some extent limited by technical issues – the need to replace data storage media and batteries every 24-48 hours, and the potential for faulty recording due to poor electrode contact. However, there has been recent development of high quality portable video-EEG home recording devices available commercially, allowing for short term day and night time (aided by infrared lighting) use. The data quality and yield of diagnostically useful attacks was comparable to hospital inpatient telemetry, with reduced costs on avoiding hospital admission²⁸.

Ictal EEG

Certain seizure types have specific ictal EEG patterns, such as 3 per second generalised spike-wave discharge in a typical absence seizure, the evolving temporal theta rhythm (5–7 Hz) in mesial temporal lobe epilepsy, high frequency discharge in tonic seizures, and irregular slow spike and wave (<2.5 Hz) in an atypical absence attack. Ictal changes can however be obscured by artefact from movement or muscle, and scalp EEG may be unchanged or unhelpful in simple partial seizures, some frontal lobe epilepsies and *epilepsia partialis continua*, mostly because the epileptogenic focus is small and anatomically circumscribed or distant from recording electrodes on the scalp. In focal epilepsies, the most important ictal EEG changes for seizure localisation occur within the first 30 seconds after the seizure onset. Broadly speaking, localised and lateralised changes are more likely to be found in temporal lobe epilepsy than in extratemporal seizures, and epileptiform or high frequency discharge tends to be seen in neocortical epilepsy, particularly when the focus is relatively superficial²⁹⁻³⁰. Frontal lobe epilepsy often shows generalised or widespread high frequency activity/slow rhythms/attenuation, as a result of rapid propagation or secondary generalisation.

The EEG and status epilepticus

EEG is essential for correct diagnosis and management of status epilepticus (SE) in convulsive and non-convulsive forms. The different electro-clinical types of SE show common EEG features, manifest as waxing and waning rhythmic or patterns or epileptiform discharges³¹.

In *convulsive status epilepticus*, EEG is used diagnostically to confirm that the patient has status and not pseudostatus, in which ictal EEG is normal, and to differentiate causes of altered mental status – ongoing seizure activity, drug-induced coma, or other encephalopathy³². In refractory convulsive status, EEG monitoring to control and guide treatment is essential once general anaesthesia has been induced, as clinical manifestations of continuing seizure activity may be subtle or absent. A typical endpoint for general anaesthesia treatment is EEG burst suppression; cessation of seizure activity or ED may be sufficient, but is less easy to define. EEG can contribute prognostic information: continuing electrographic status is associated with worse outcome in convulsive status³³, and some studies have shown that periodic epileptiform discharges are associated with poorer outcome independent of aetiology of status³⁴.

Non-convulsive status epilepticus (NCSE) covers a range of conditions, which have variable clinical features and aetiological bases: generalised absence status, *de novo* absence status, simple partial status epilepticus, complex partial status, electrographic status with subtle clinical manifestations, and electrical status epilepticus in sleep³⁵. EEG patterns described in NCSE include continuous spike-wave discharge, discrete localised electrographic seizures, diffuse slow activity with or without spikes, and periodic/repetitive ED. Electrographic diagnosis is relatively easy in generalised absence status, when the prolonged state of altered consciousness is accompanied by generalised 3 Hz spike-wave discharge. EEG confirmation is usually straightforward in persistent electrographic status after control of convulsive status, and in children with ESES. More problematic are cases of simple partial status, in which the EEG can be unchanged or non-specific; or in acute cerebral

damage due to anoxia, infection or trauma, when EEG abnormalities, particularly repetitive complexes, may be due to the primary pathology³⁶.

Role of neurophysiology in evaluation of patients for epilepsy surgery

Inter-ictal and ictal EEG are pivotal in pre-surgical assessment, in conjunction with neuroimaging and neuropsychological evaluation, but the importance of neurophysiological investigation depends in part on the surgical procedure. It is high in resective surgery (lesionectomy, lobectomy) and multiple sub-pial transection, moderate in hemispherectomy, and low in functional procedures (callosotomy, vagal nerve stimulation) except to exclude the option of resection.

Neurophysiological assessment in pre-surgical evaluation is aimed at:

- Ensuring that the individual has epileptic seizures (4-10% of patients in surgical programmes have co-morbid psychogenic non-epileptic seizures)
- Characterisation of electro-clinical seizure features, and show concordance with other data (MRI, functional imaging, psychometry)
- Demonstration of epileptogenicity in the presumed pathological substrate of refractory epilepsy
- Identification of possible other epileptogenic foci
- Assessment of cortical function when pathology is in or close to eloquent cortex.

While most epilepsy surgery candidates can be adequately investigated by scalp inter-ictal and ictal EEG, some require invasive neurophysiological studies. The proportion who do in a given epilepsy surgery centre depends on complexity of case mix, availability of non-invasive localising investigations such as SPECT, PET, MEG, and fMRI-EEG. Invasive EEG utilises depth electrodes (rigid or flexible multi-contact wires inserted under stereotactic MRI guidance, most appropriate for deep lying foci, and with the disadvantage of sampling only small areas of brain), and sub-dural electrodes (strips or grids, inserted via a craniotomy or burr hole, and recording from larger superficial cortical regions). Cortical stimulation can be performed with either type of invasive EEG electrode. Electrode selection and placement is determined by location of the epileptogenic zone. There is increasing use of multiple depth electrodes by stereotactic placement (stereoEEG) to define the epileptogenic zone as 3D distributed networks, rather than a focal area with contiguous spread as with sub-dural electrodes. The usual indications for invasive EEG are dual or possibly multiple potential epileptogenic pathologies, bilateral hippocampal sclerosis, and focal lesions in eloquent cortex. Invasive EEG is also undertaken when underlying structural pathology is not evident on neuroimaging, but a plausible hypothesis as to location of the epileptogenic region has been generated by other investigations.

Specialised neurophysiological techniques

A number of techniques have been developed to optimise selection of candidates for epilepsy surgery, and to enhance understanding of the anatomical-pathophysiological basis of epilepsy. These include analytical methods to study seizure propagation (small time differences in EEG signals, cross-correlation, chaos theory); source localisation of the generators of epileptic foci using EEG, magnetoencephalography and combined functional MRI/EEG; DC recording; measurement of cortical excitability through magnetic brain stimulation³⁷; and anticipation/prediction of seizures using linear and non-linear analysis of EEG signals³⁸. Recent studies have used invasive EEG with

high sampling rates (~2000Hz) to record high frequency oscillations (HFO) at 80–200 Hz (ripples) and 200–600Hz (fast ripples), closely related to seizure onset zones – the origin of clinical seizures. Removal of tissue exhibiting HFOs in drug resistant focal epilepsy patients has been correlated to good post surgical outcome, suggesting their use as a more reliable biomarker of epileptogenicity than interictal or ictal spikes³⁹. These techniques are of considerable theoretical interest, but at present, their application is largely confined to specific areas of research.

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CHAPTER 21

Neuroimaging of the epilepsies

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Introduction

Much progress has been made over the last 20 years in the structural and functional imaging of the brain in epilepsy. The correlation of structure with function is essential in the understanding of the epilepsies and epileptic seizures, which may have a structural basis.

MAGNETIC RESONANCE IMAGING

The superiority of magnetic resonance imaging (MRI) over X-ray computed tomography (CT) scanning in terms of sensitivity and specificity for identifying the aetiology of epilepsy in both adults and children is firmly established. The most common abnormalities identified are hippocampal sclerosis (HS), malformations of cortical development (MCD), vascular malformations, tumours, and acquired cortical damage. X-ray CT, however, may be preferred to MRI if a patient is disturbed or acutely unwell, as the patient is more accessible during the procedure. An X-ray CT scan is also valuable for the investigation of possible acute intracranial haematomas and skull fractures, and if there is a contraindication to MRI such as a cardiac pacemaker or cochlear implants. CT is also useful as a supplement to MRI for clarification of possible intracranial calcification that is not shown easily by MRI.

The principal clinical applications of MRI are to identify the structural basis of epilepsy and patients who are suitable for surgical treatment. Rapid advances are being made in MRI techniques so that patients who were previously regarded as being 'MRI negative' may have relevant abnormalities, which can be identified with contemporary optimal imaging.

MRI epilepsy protocol

Indications for neuroimaging of patients with epilepsy

The Neuroimaging Commission of the International League Against Epilepsy has produced recommendations for this. The rationale for imaging the brains of patients developing epilepsy is first to identify underlying pathologies such as vascular lesions, infections and tumours that require specific therapy; and second to assist the formulation of syndrome and aetiological diagnoses¹. Further recommendations have been made for patients with refractory seizures² and for functional neuroimaging³.

In the non-acute situation an MRI scan should include T2-weighted, proton density and fluid attenuated inversion recovery (FLAIR) sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible. There should also be a T1-weighted volume acquisition with a partition size of 1.5 mm or less, to allow reformatting in any orientation and three-dimensional reconstruction of the data set. The FLAIR sequence produces images

in which parenchymal lesions have high signal and CSF gives low signal. This may help in the differential diagnosis of areas of high signal on T2-weighted images and increase the conspicuity of lesions, but does not improve the identification of heterotopias⁴⁻⁷. In the first two years of life, incomplete myelination results in poor grey-white matter contrast, making identification of cortical abnormalities difficult, and in these cases MRI may need to be repeated after 1-2 years.

In an acute situation when seizures occur in the context of a neurological insult, X-ray CT is an appropriate initial investigation if MRI is not readily available or not possible for technical reasons, for instance if the patient has a cardiac pacemaker or requires attention during the scan. Recent improvements in the design and manufacture of pacemakers and vagal nerve stimulators have improved MRI compatibility although safety issues at higher field strength remain an issue.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diagnosis of idiopathic generalised epilepsy or benign rolandic epilepsy of childhood with centrotemporal spikes, who go into early remission. MRI is particularly indicated in patients with one or more of the following:

- Onset of partial seizures, at any age
- Onset of generalised or unclassified seizures in the first year of life, or in adulthood
- Evidence of a fixed deficit on neurological or neuropsychological examination
- Difficulty obtaining seizure control with first-line antiepileptic drugs (AEDs)
- Loss of seizure control, or a change in the pattern of seizures.

In situations in which access to MRI is limited, essential indications for MRI are:

- Patients with partial or secondarily generalised seizures, and apparently generalised seizures, that are not controlled with AEDs
- Patients who develop progressive neurological or neuropsychological deficits.

A recent survey in the UK shows that optimal practice is not applied universally⁶, and in a study in Germany, the quality of MRI scans obtained in community hospitals was significantly less than those obtained at an epilepsy centre⁸.

Presurgical candidates

Patients who are being considered for surgical treatment merit the most sophisticated MR imaging that is available and may also benefit from functional imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT). Identification of a structural lesion, however, does not always indicate the site of seizure origin. Clinical, EEG and other data all need to be considered.

A typical presurgical MRI protocol would be:

- Volume acquisition T1-weighted data set that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covers the whole brain in 0.9 mm partitions. This sequence produces approximately cubic voxels, allowing for reformatting in any orientation, subsequent measurement of hippocampal morphology and volumes, and for three-dimensional reconstruction and surface rendering of the brain;

- Oblique coronal spin-echo sequence, with proton density (TE = 30), heavily T2-weighted (TE = 90 or 120) and FLAIR acquisitions that are orientated perpendicular to the long axis of the hippocampus, to demonstrate any increase in T2-weighted signal intensity.

Structural cerebral abnormalities underlying epilepsy identified with MRI

Hippocampal sclerosis

Hippocampal sclerosis (HS) is the single most common pathology underlying refractory focal epilepsy, and is amenable to surgical treatment. The hippocampus is best visualised in two planes: along its long axis and orthogonal to this. These imaging planes may be readily determined on a sagittal scout image: the axial plane being in the line joining the base of the splenium of the corpus callosum to the inferior, posterior border of the frontal lobe and the coronal plane being perpendicular to this, parallel to the anterior border of the brainstem.

The features of HS identified by MRI are hippocampal atrophy, demonstrated with coronal T1-weighted images, and increased signal intensity within the hippocampus on T2-weighted spin-echo images⁹, decreased T1-weighted signal intensity and disruption of the internal structure of the hippocampus¹⁰. Atrophy of temporal lobe white matter and cortex, dilatation of the temporal horn and a blurring of the grey-white matter margin in the temporal neocortex variably accompany HS¹¹⁻¹⁴. Entorhinal cortex atrophy may also occur in TLE with normal hippocampi¹⁵.

Sophisticated and computationally expensive analyses of three-dimensional hippocampal surface shape, and specifically deformation, have shown distinct regional changes, for example, in the CA1 region in hippocampal sclerosis and in the medial aspect of the head of the hippocampus in patients with temporal lobe epilepsy and normal conventional MRI. Moreover, diffuse atrophy or contralateral hippocampal abnormalities suggested a poor post-operative outcome¹⁶.

Quantitative MRI assessment of the hippocampus

Assessment of hippocampal atrophy can be improved by measuring hippocampal volumes. The use of contiguous thin slices enhances the reliability of measurements and permits localisation of atrophy along the length of the hippocampus¹⁷. Hippocampal volumetry is demanding and time-consuming, requiring a skilled operator and a post-processing computer. In clinical practice, hippocampal asymmetry of 20% or more is reliably visually apparent to skilled neuroimaging specialists, but lesser degrees of asymmetry require quantification¹⁸. Attempts have been made to automate hippocampal volume estimations and although voxel-based approaches have given promising results, they remain inferior to expert manual assessment^{19,179,180}.

The T2-weighted signal intensity may be quantified by measurement of hippocampal T2 relaxation time (HT2) and this is a useful identifier of hippocampal pathology. HS may be of varying severity along the length of the hippocampus, and may be confined to the anterior part of the head²⁰. A T2 relaxometry technique incorporating a FLAIR sequence obviates possible contamination from high T2 in cerebrospinal fluid (CSF)²¹. Hippocampal volume corrected for intracranial volume and HT2 are useful for identifying contralateral hippocampal abnormality²². The same technique is useful for identifying amygdala pathology²³.

Malformations of cortical development

Malformations of cortical development (MCD) are increasingly being recognised in patients with seizure disorders previously regarded as cryptogenic. The range of MCD identified with MRI include schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal grey matter heterotopias, bilateral subcortical laminar heterotopia, tuberous sclerosis, focal cortical dysplasia and dysembryoplastic neuroepithelial tumours (DNTs). DNTs are benign developmental tumours and commonly underlie refractory partial seizures. The

features are of a focal, circumscribed cortical mass that may indent the overlying skull and also extend subcortically, with low signal intensity on T1-weighted images, high signal on T2-weighted images that is similar to CSF, and slightly higher signal intensity in the lesion than CSF on proton density images. Cyst formation and enhancement with gadolinium may occur. Calcification is present in some cases and may be more readily demonstrated with X-ray CT. Confident differentiation from low-grade astrocytomas and ganglioglioma is not possible by MRI²⁴.

Hypothalamic hamartomas, sometimes associated with gelastic epilepsy, precocious puberty and cognitive impairment, are clearly demonstrable using MRI²⁵. More subtle abnormalities such as focal nodular heterotopia and band heterotopia may only be apparent if optimal MRI techniques are used. Band heterotopia 'double cortex' is an example of a generalised MCD that may be present in patients with mild epilepsy and normal intellect.

Focal cortical dysplasia may result in refractory partial seizures. The possibility of surgical treatment means its identification with MRI has important consequences. Focal cortical dysplasia is not always identified with conventional MRI and may be more easily identified on a FLAIR sequence^{6,26,181}, by reconstructing the imaging dataset in curvilinear planes, by quantitative assessment of signal and texture²⁷ and by sulcal analysis²⁸.

Cavernomas

Cerebral cavernomas commonly underlie epilepsy and surgical removal carries up to a 70% chance of subsequent seizure remission. Cavernomas are often not identified on X-ray CT, but are readily apparent on MRI. Cavernomas are circumscribed and have the characteristic appearance of a range of blood products. The central part contains areas of high signal on T1- and T2-weighted images, reflecting oxidised haemoglobin, with darker areas on T1-weighted images due to deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T2-weighted image. There may be calcification, which usually appears dark on T1- and T2-weighted images. There is no evidence of arteriovenous shunting. Arteriovenous malformations with high blood flow have a different and distinctive appearance.

Granulomas

Worldwide, the commonest causes of refractory focal epilepsy are cysticercosis and tuberculomas. These lesions have characteristic appearances on MRI that evolve with time and which, unless calcified, may resolve and be regarded as 'disappearing lesions'²⁹.

Longitudinal studies of the effect of epilepsy on the brain

Voxel and anatomically-based methods may be applied in longitudinal studies to identify subtle changes in the brain and to determine the effects of epilepsy. The majority of previous cross-sectional studies have inferred that more severe hippocampal damage is associated with a longer duration of epilepsy and a greater number of seizures. Longitudinal studies, however, are necessary to ascribe cause and effect. Two recent studies have suggested atrophy of the hippocampus occurring over three years of active epilepsy in patients attending epilepsy clinics^{30,31}.

A large community-based study has shown that those with a history of a prior neurological insult had smaller neocortical volumes and an accelerated rate of brain atrophy, and that in patients with newly diagnosed epilepsy without a history of prior insult the rate of atrophy was no different from age-matched controls. Patients with chronic epilepsy, however, were more likely to have had significant loss of neocortical, hippocampal or cerebellar volume over 3.5 years³². Further, on a more sensitive voxel-based analysis, 54% of those with chronic epilepsy, 39% of those with newly diagnosed seizures and 24% of controls had areas of brain volume loss³³. These studies implied that secondary brain damage might occur in the context of chronic epilepsy. The next step is to identify the aetiological factors and how to intervene to prevent this process.

Advanced structural MRI techniques

Diffusion-weighted imaging is very sensitive in the detection of early ischaemic changes, and shows changes in status epilepticus³⁴. Diffusion tensor imaging (DTI) reveals lesions found with conventional MRI and also abnormalities that are not visualised on routine sequences³⁵⁻³⁷. However, these occult abnormalities may be the result of and not the cause of chronic epilepsy³⁸. Tractography is a derivation of diffusion tensor imaging that allows identification of nerve fibre tracts within the brain, and demonstrates the structural basis of connectivity between brain regions³⁹. Using tractography to interrogate the visual pathways it is possible to predict the occurrence and extent of a visual field defect following anterior temporal lobe resection (ATLR). A recent study found that the anterior extent of Meyer's loop ranged from 24–43 mm from the temporal pole. Significant post-operative visual field defects were only seen in those individuals in whom the anterior aspect of Meyer's loop was less than 35 mm from the temporal pole⁴⁰. Pre- and intra-operative tractography has also been used to demonstrate the optic radiation in patients having temporal lobe resection and to predict the extent of visual field defect⁴¹. Similar studies have been reported in patients with tumours and may aid surgical planning of patients undergoing lesionectomy near eloquent cortex. Tractography has the potential to demonstrate the structural reorganisation of networks involved in memory and language that mirror changes in cerebral function. In a combined fMRI-tractography study, controls and right TLE patients had a left-lateralised pattern of both language-related activations and associated white matter organisation. Left TLE patients had reduced left-hemisphere and increased right-hemisphere white matter pathways, in comparison to controls and right TLE patients. Subjects with more lateralised functional activation had more lateralised white matter pathways⁴². The arcuate fasciculus was shown to be larger in the speech dominant hemisphere, and the left-right asymmetry was reduced if there was dominant hemisphere pathology⁴³. More recent developments in diffusion imaging methods such as neurite orientation dispersion and density imaging or diffusional kurtosis imaging, which provide more detail on tissue microstructure, increase sensitivity for the detection of focal cortical dysplasia¹⁹¹.

Other promising new MRI sequences include magnetisation transfer ratio imaging⁴⁴, double inversion recovery imaging and fast FLAIR T2-mapping. Ultra-fast low-angle rapid acquisition and relaxation enhancement is a sequence that may be useful for patients who are restless and can only tolerate short studies⁴⁵. A recently implemented MR sequence called 'periodically rotated overlapping parallel lines with enhanced reconstruction' ('PROPELLER') has an excellent in-plane resolution of 0.5 mm and is therefore able to demonstrate internal hippocampal structures within a clinical acceptable time-frame⁴⁶. This may allow the detection of subtle hippocampal changes in patients with temporal lobe epilepsy.

Continuous arterial spin labelling perfusion MR imaging can detect asymmetries in mesial temporal lobe perfusion inter-ictally in patients with TLE⁴⁷ and may identify focal cortical dysplasia^{182,190}

Improved gradient performance is anticipated to improve speed and spatial resolution. Phased array surface coils improve signal-to-noise ratio in superficial cortex and hippocampal regions and this may lead to improved spatial resolution. Imaging at high field strengths may also improve spatial resolution. 3T MRI scanners are now available as mature clinical instruments and may increase the clinical yield by up to 20%^{48,183}. The utility of higher field strength scanners, up to 7T, is also being evaluated and may provide further insights into subtle structural abnormalities¹⁸⁴.

Voxel-based morphometry may demonstrate areas of hippocampal atrophy in individual patients with clear-cut hippocampal sclerosis⁴⁹ but for the detection of occult abnormalities in individual patients it appears to be relatively insensitive at thresholds that do not give false positive results⁵⁰. These methods are complemented by anatomical atlases, which allow quantification of brain imaging data on a lobar and sub-lobar basis^{51,52}. Analysis of the texture of the neocortex on a T1-weighted volume scan may give increased sensitivity to identify focal cortical dysplasia²⁷.

Curvilinear reconstructions may increase the visibility of subtle neocortical lesions⁵³. Three-dimensional reconstruction of the neocortex may assist visualisation of abnormalities and surgical planning⁵⁴, and this can now be automated⁵⁵.

FUNCTIONAL MRI

Ictal and inter-ictal epileptiform activity

Activation of eloquent cortex has been shown in patients with frequent partial seizures and in patients undergoing epilepsy surgery who had invasive EEG evaluation, the ictal-onset phase-related maps were concordant with the presumed seizure onset zone for all patients. The most statistically significant haemodynamic cluster within the presumed seizure onset zone was between 1.1 and 3.5 cm from the invasively defined seizure onset zone. Resection of this region was associated with a good surgical outcome¹⁸⁵.

Focal increases in cerebral blood delivery have been identified in patients with frequent inter-ictal spikes⁵⁶⁻⁵⁸. Continuous recording of EEG and functional MRI (fMRI) is possible, following introduction of methods to remove the artifact on the EEG trace caused by the fMRI acquisition, and results in much more detail and analysis of the time course of haemodynamic changes^{59,60}. However, even in well-selected patients, approximately 50% do not exhibit inter-ictal epileptiform discharges during the 10-60 minute EEG/fMRI study. Of the remaining patients, approximately 50-90% lead to significant signal changes which are concordant with electroclinical data^{61,62,186}. These results may be used to re-evaluate patients who have, for example, been previously rejected for epilepsy surgery⁶³.

The most recent and largest of these studies reported 76 patients with refractory focal epilepsy, 33 of whom had extratemporal lobe epilepsy. No discharges were seen during the 35-60 minute acquisition in 64% of the patients. The mean number of discharges during the recording in the remaining patients was 89.3. Ten patients underwent surgical treatment, seven of whom achieved seizure freedom. In six of these seven patients, the area of resection included the area of maximum BOLD (blood-oxygen-level dependent) signal increase. Interestingly, in the remaining three patients who continued to have seizures after surgery, the areas of maximal BOLD activation did not overlap with the resected area suggesting that EEG/fMRI may possess a negative predictive value for a good surgical outcome, that is, a lack of concordance with other localising investigations may predict a poor postoperative outcome⁶⁴.

The interrogation of the EEG/fMRI data for typical spike-related haemodynamic responses in patients without spikes during the recording period may also provide useful localising information and improve the yield of EEG/fMRI studies¹⁸⁷.

The feasibility of combining fMRI with intracranial EEGs is being studied⁶⁵. As EEG-fMRI covers the whole brain, and as intracranial EEG has very limited spatial sampling, the BOLD changes may assist in the interpretation of intracranial EEG data. This is particularly relevant if the irritative and seizure onset zones are not being sampled directly by the EEG contacts, but these are detecting the propagation of epileptic activity, as the fMRI data can be examined for BOLD changes prior to the first detected EEG changes.

Localisation and lateralisation of cognitive function

An important use of fMRI in patients with epilepsy is to delineate areas of brain that are responsible for specific functions, such as the primary sensory and motor cortex, and to identify their anatomical relation to areas of planned resection^{66,67}. In patients with cerebral lesions, the localisation

of cognitive activation may differ from the pattern in normal subjects. These data may be helpful in the planning of neocortical resections of epileptic foci, in order to minimise the risk of causing a fixed deficit.

Lateralisation of language function may also be accomplished using fMRI⁶⁸. There was a strong correlation between language lateralisation measured with the carotid amyntal test, and using fMRI with a single-word semantic decision task⁶⁹ and other fMRI language studies have generally concurred with carotid amyntal testing⁷⁰. The high proportion (33%) of left-TLE patients showing bilateral or right hemispheric language-related lateralisation with fMRI implies plasticity of language representation in patients with intractable TLE⁷¹.

fMRI results do not always accord with carotid amyntal data⁷². A combination of language tasks may be more reliable than a single task^{73,74}. Artefacts and technical difficulties may adversely affect both methods and false lateralisations may occur⁷⁵. Further, identification of the areas of brain involved in language is not the same as determining if someone can speak when half of the brain is anaesthetised.

As well as predicting the lateralisation of language function, fMRI may localise cerebral areas involved in language⁷⁶⁻⁷⁸. For example, in a fMRI study of healthy right-handed subjects, tasks of reading comprehension activated the superior temporal gyri, and verbal fluency and verb generation tasks activated the left inferior and middle frontal gyri and left insula⁷⁹. Generally, verbal fluency usually gives stronger and wider activations than verb generation⁸⁰. These data may assist in planning surgical resections in the language-dominant hemisphere. There are, however, important caveats. Absence of activation on one language task does not guarantee that that part of the brain is inert. Conversely, an area that is activated may have only a peripheral and non-essential role in verbal communication.

Left temporal lobe epilepsy is associated with increased likelihood of expressive language activation in the right frontal lobe, and atypical dominance is more likely with early onset of epilepsy⁸¹. In patients with lesions close to Broca's area expressive language function may be shown in perilesional cortex⁸². There is considerable heterogeneity of this effect between individuals, related to the underlying pathology⁸³, which needs to be taken into account when planning surgical treatment close to language areas. There has been concern that language lateralisation with fMRI may be less reliable in the presence of structural lesions⁸⁴, and caution is required with clinical interpretation.

Up to 40% of individuals will have significant language deficits, particularly a decline in naming ability after a left anterior temporal lobe resection. Preoperative language fMRI predicted significant language decline, with greater activation in the left hemisphere, particularly the temporal lobe, being associated with greater risk of post-operative impairment⁸⁵.

Following temporal lobe resection there is evidence of both intra- and interhemispheric reorganisation of language functions⁸⁶. After left temporal lobe resection, reading sentences activated the right inferior frontal and right temporal lobes, in addition to the remaining left temporal lobe⁸⁷.

Decline of memory function following anterior temporal lobe resection, particularly of verbal memory after left-sided ATR, is a major concern. Several studies have investigated the role of fMRI in predicting the effects of ATR on memory⁸⁸⁻⁹³. Most focused on the prediction of verbal memory decline; only a few investigated visual memory decline after non-dominant ATR. Patients with greater ipsilateral than contralateral medial temporal lobe activation on fMRI memory activation studies had greater memory decline following temporal lobe resection for both verbal memory decline following dominant temporal lobe resection, and for non-verbal memory decline following

non-dominant temporal lobe resection. This investigation suggests that preoperative memory fMRI may be a useful non-invasive predictor of postoperative memory change following temporal lobe resection⁹³.

The choice of paradigm is important in determining activation patterns. Greater left anterior hippocampal activation on word encoding was predictive of greater post-operative decline in verbal memory after left-sided resection, and greater right anterior hippocampal activation on face encoding predicted greater decline in design learning after right-sided resection⁹⁴. Also, greater left than right posterior hippocampal activation correlated with better postoperative verbal memory outcome and greater right than left posterior hippocampal activation correlated with better visual memory outcome. This suggests that reorganisation of function to the posterior hippocampus is associated with better preservation of memory following anterior resection¹⁸⁸. This was explored further with a longitudinal study of memory fMRI after temporal lobe surgery and again postoperative changes were identified in the memory-encoding network in both left and right temporal lobe epilepsy patients across both verbal and visual domains. Three months after surgery, compensatory posterior hippocampal reorganization that occurs appears to be transient and inefficient. However, engagement of the contralateral hippocampus 12 months after surgery represented efficient reorganization in both patient groups, suggesting that the contralateral hippocampus contributes to memory outcome 12 months after surgery¹⁸⁹.

MAGNETIC RESONANCE SPECTROSCOPY

The metabolites which are detectable using proton spectroscopy (¹H MRS) depend on the conditions used for the acquisition. In epilepsy studies *in vivo*, the principal signals of interest have been those from N-acetyl aspartate (NAA), creatine + phosphocreatine (Cr), choline-containing compounds (Cho), and lactate (Lac). There is evidence that NAA is located primarily within neurons and precursor cells and a reduction of NAA signal is usually regarded as indicating loss or dysfunction of neurons. Cr and Cho are found in both neurons and in glia.

MRS in temporal lobe epilepsy

In TLE caused by HS, MRS showed reduction of NAA and increases of choline-containing compounds, creatine + phosphocreatine, reflecting neuronal loss or dysfunction and astrocytosis⁹⁵. Analysis of individual patients showed a reduced NAA/choline + creatine ratio on the side of the focus in 88%, with 40% having bilateral abnormalities. Quantitative short echo time MRS showed the association of HS with low NAA and raised myoinositol, and also an elevation of glutamate and glutamine in epileptic hippocampi that were structurally normal⁹⁶. The implication from these data was that there is neuronal loss or dysfunction and astrocytosis in the temporal lobes of patients with TLE. Abnormalities of metabolite profiles may be found in temporal lobes with normal MRI⁹⁷⁻⁹⁹ and bilateral abnormalities have been noted in up to 50% of patients with apparently unilateral structural abnormality¹⁰⁰, indicating that MRS may be more sensitive for detecting pathology. The role of MRS in predicting outcome is not clear: in one study of patients with TLE and normal MRI, a lower NAA/choline + creatine was found in those who did not become seizure free¹⁰¹. NAA was not reduced in the hippocampi of patients with neocortical epilepsy, either ipsilateral or contralateral to the focus¹⁰², suggesting that hippocampal dysfunction is not a feature of neocortical epilepsy. Mesial TLE was associated with reductions of NAA in frontal grey and white matter, which is consistent with other data suggesting more widespread involvement¹⁰³.

Proton (¹H) MRS in extratemporal epilepsies

A multivoxel ¹H MRS imaging (MRSI) study reported reduced NAA in frontal lobes ipsilateral to frontal lobe epileptic seizures and the decrease in NAA was inversely related to seizure frequency,

suggesting that a higher seizure frequency is associated with more neuronal dysfunction or loss¹⁰⁴.

Malformations of cortical development

Reduced NAA/choline and NAA/creatine have been shown in focal cortical dysplasia¹⁰⁵ and other malformations of cortical development¹⁰⁶. Quantitative short echo time MRSI, with correction for partial volume effects, has shown that metabolic abnormalities were heterogeneous and more extensive than the structural lesions evident on MRI¹⁰⁷. A post-ictal rise in lactate has been shown using MRSI in the ipsilateral temporal lobe in patients with unilateral TLE¹⁰⁸. An elevation of cerebral lactate has been noted during and for a few hours after complex partial seizures, with no change in NAA¹⁰⁹. MRS has shown elevated lactate, decreased NAA and elevated choline during status epilepticus. Subsequently, lactate and choline returned to normal, whereas the NAA level remained reduced, implying neuronal loss or dysfunction^{110,111}.

GABA

GABA is the principal inhibitory neurotransmitter in the brain, acting at up to 40% of synapses, with a resting concentration of 1-2 mmol/L and a major role in regulation of seizure activity. Proton MRS, using spectral editing, can identify cerebral GABA *in vivo* and estimate the rise in cerebral GABA concentrations that occurs after administration of vigabatrin¹¹², gabapentin¹¹³ and topiramate¹¹⁴. Low GABA concentrations have been associated with continued seizure activity¹¹⁵. Low GABA levels were associated with poor seizure control in patients with complex partial seizures, but not in juvenile myoclonic epilepsy. Higher homocarnosine concentrations were associated with better seizure control in both types of epilepsy¹¹⁶.

Glutamate and glutamine

Glutamate is the principal excitatory neurotransmitter in the brain and responsible for mediating excitotoxicity and initiating epileptic activity¹¹⁷. Glutamate is also an intermediary metabolite, and present at a concentration of 8-12 mmol/L. Aspartate, also an excitatory transmitter, is present at a concentration of 1- mmol/L. Discrimination between glutamate and glutamine *in vivo* on clinical scanners requires spectral modelling, because of the large number of coupled overlapping peaks and the limited achievable spectral resolution¹¹⁸.

MRS using short echo times (30 msec), voxels tailored to individual hippocampi and quantitative assessment has shown reduced NAA and increased myoinositol (reflecting gliosis) in epileptogenic sclerotic hippocampi, and similar but less severe abnormalities contralaterally⁹⁶. In patients with TLE and normal MRI, the MRS profile was characterised by elevation of glutamate and glutamine. An increased concentration of combined glutamate + glutamine was noted following focal status epilepticus, with resolution at three months, but persistence of low levels of NAA¹¹⁹. Malformations of cortical development, such as heterotopia and polymicrogyria, have also shown changes in glutamate, glutamine and GABA concentrations consistent with abnormal metabolism of both inhibitory and excitatory neurotransmitters¹⁰⁶.

SINGLE PHOTON EMISSION COMPUTERISED TOMOGRAPHY

Single photon emission computerised tomography (SPECT) is principally used in the investigation of the epilepsies to image the distribution of cerebral blood flow (CBF). The most commonly used SPECT tracers for imaging CBF are ^{99m}Tc-hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (ECD, bicsate). ^{99m}Tc-HMPAO is given by vein and 70% brain uptake occurs in one minute. The subsequent image is stable for six hours, as after crossing the blood-brain barrier ^{99m}Tc-HMPAO reacts with intracellular glutathione, becoming hydrophilic and

so is much less able to recross the blood-brain barrier. Radio-labelled ECD is stable for six hours, easing study of brief ictal events¹²⁰.

Inter-ictal SPECT studies

It was established in the 1980s that the marker of an epileptic focus studied inter-ictally in adults and children with SPECT is a region of reduced CBF, but it was soon noted that the results were not reliable. Lobar localisation (e.g. frontal versus temporal) has been more difficult with, in one large representative series, correct localisation in 38% in inter-ictal studies of patients with unilateral temporal lobe EEG focus¹²¹. Localisation with inter-ictal SPECT is more difficult in patients with extratemporal epilepsy^{122,123}. In a blinded comparative study, inter-ictal SPECT was less effective at lateralising the focus of TLE than MRI, with correct lateralisation in 45% compared to 86%. In consequence, inter-ictal SPECT has little place in the routine investigation of patients with epilepsy.

Ictal and post-ictal SPECT studies

The increase in CBF associated with a seizure may be detected using SPECT and may provide useful localising information in patients with partial seizures. An injection of ^{99m}Tc-HMPAO at the time of a seizure results in an image of the distribution of CBF 1–2 minutes after tracer administration. The general pattern is of localised ictal hyperperfusion, with surrounding hypoperfusion, that is followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the inter-ictal state. Combined data from inter-ictal and ictal SPECT scans give a lot more data than inter-ictal scans alone and may be useful in the evaluation of both temporal and extratemporal epilepsy. In complex partial seizure disorders, the epileptic focus has been identified in 69–93% of ictal SPECT studies. A meta-analysis of published data showed that in patients with TLE, the sensitivities of SPECT relative to diagnostic evaluation were 0.44 (inter-ictal), 0.75 (post-ictal) and 0.97 (ictal)¹²⁴.

In temporal lobe seizures, the occurrence of contralateral dystonic posturing was associated with an ictal increase in CBF in the basal ganglia ipsilateral to the focus¹²⁵. A characteristic feature of temporal lobe seizures is an initial hyperperfusion of the temporal lobe, followed by medial temporal hyperperfusion and lateral temporal hypoperfusion¹²⁶.

Ictal ^{99m}Tc-HMPAO scans may be useful in the evaluation of patients with extratemporal seizures and unremarkable MRI¹²⁷. Asymmetric tonic posturing, contralateral head and eye deviation and unilateral clonic jerking were associated with an ictal increase in CBF in the frontocentral, medial frontal or dorsolateral areas¹²⁷. Varying patterns have been seen in patients with autosomal dominant frontal lobe epilepsy¹²⁸.

The coregistration of post-ictal SPECT images with a patient's MRI improves anatomical determination of abnormalities of CBF¹²⁹. A greater advance, however, has been the coregistration of inter-ictal with ictal or post-ictal SPECT images, to result in an 'ictal difference image' that may be coregistered with an individual's MRI. This technique enhances objectivity and the accuracy of data interpretation^{130,131}. More recently, it has been shown that voxel-based analysis of SPECT blood flow studies, specifically of the difference between ictal and inter-ictal cerebral blood flow as a Z-score of the interscan variation of SPECT scans, was more accurate than just thresholding the subtraction images¹³².

Ictal SPECT may be useful as a non-invasive presurgical method of investigation by optimising the placement of intracranial electrodes to define sites of seizure onset, but there must be caution as the technique may identify sites of seizure spread, rather than the site of onset¹³³. Ictal ^{99m}Tc-HMPAO scans must always be interpreted with caution. Simultaneous video-EEG is essential

to determine the relationship between the onset of a seizure and tracer delivery; without this there is the risk of confusing ictal and post-ictal data. Further, spread to other areas of the brain, such as the contralateral temporal lobe, may occur within seconds of seizure onset and so an image of cerebral blood flow distribution 1–2 minutes after the onset of a seizure may indicate other than the site of onset.

Until recently, ^{99m}Tc-HMPAO had to be constituted immediately prior to injection, resulting in a delay of up to one minute. A preparation has now been developed which is stabilised with cobalt chloride. This allows the labelled tracer to be prepared in advance and injected into a patient at any time over the subsequent six hours. The advantage of this development is that the interval between seizure onset and tracer delivery to the brain can be significantly reduced. An alternative is to use ready constituted ^{99m}Tc-ECD, or bicesate, which is stable for several hours, may be injected within 2–20 seconds of seizure onset and demonstrates a focal increase in CBF¹³⁴. The interval between seizure onset and injection may also be shortened by the use of an automated injection device that may be activated by the patient when they detect the beginning of a seizure^{135,136}. Extratemporal seizures may be very brief, increasing the need for injection of blood flow tracer as soon as possible after the start of a seizure. With the inevitable interval between injection and fixation of the tracer in the brain, however, it may not be possible to obtain true ictal studies.

In conclusion, inter-ictal SPECT imaging of CBF is only moderately sensitive and ictal SPECT improves the yield. The place of the investigation is in the presurgical work-up of patients with refractory partial seizures and normal MRI scans, in order to generate a hypothesis that may then be tested with intracranial EEG recordings.

POSITRON EMISSION TOMOGRAPHY STUDIES OF CEREBRAL BLOOD FLOW AND GLUCOSE METABOLISM

Positron emission tomography (PET) may be used to map cerebral blood flow, using ¹⁵O-labelled water, and regional cerebral glucose metabolism using ¹⁸F-deoxyglucose (¹⁸FDG). PET produces quantitative data with superior spatial resolution to SPECT. PET data should always be interpreted in the light of high quality anatomical MRI, providing a structural-functional correlation. The development of programmes to coregister MRI and PET datasets on a pixel-by-pixel basis has been fundamental to making these correlations. Statistical parametric mapping has been shown to be useful in the evaluation of ¹⁸FDG-PET scans for clinical purposes, with the advantages of allowing a rapid and objective evaluation¹³⁷. In addition, quantitative analysis of data, with correction for partial volume effects add a further useful dimension to the analysis, and this is facilitated by the use of a template to objectively delineate multiple volumes of interest⁵¹.

An epileptogenic focus, studied inter-ictally, is associated with an area of reduced glucose metabolism, and reduced blood flow that is usually considerably larger than the pathological abnormality. Comparison of ¹⁸FDG-PET scans with ¹¹C-flumazenil (FMZ) scans^{138–140} indicate that neuronal loss is confined to a more restricted area than the region of reduced metabolism.

Ictal PET scans can only be obtained fortuitously, because of the two-minute half-life of ¹⁵O and the fact that cerebral uptake of ¹⁸FDG occurs over 40 minutes after injection, so that cerebral glucose utilisation data will reflect an amalgam of the ictal and post-ictal conditions. The place of ¹⁸FDG-PET as a tool for localising an epileptic focus has been greatly reduced following developments in MRI, as the finding of a definite focal abnormality with the latter technique, such as HS, renders an ¹⁸FDG-PET scan superfluous¹⁴¹. The place of the investigation is in the presurgical work up of patients with refractory partial seizures and normal or non-definitive MRI scans, or if data are discordant, in order to generate a hypothesis that may then be tested with intracranial EEG recordings.

Temporal lobe epilepsy

Several studies of ¹⁸F-DG-PET have found a 60–90% incidence of hypometabolism in the temporal lobe inter-ictally in adults and children with TLE. The results of comparative studies depend critically on the relative sophistication of the techniques used. In a comparative study of patients with TLE it was concluded that ¹⁸F-DG-PET data did not provide clinically useful data if the MRI findings were definite, but had some additional sensitivity¹⁴². This was confirmed in a more recent study in which ¹⁸F-DG-PET data correctly lateralised the seizure focus in 87% of patients with TLE and normal conventional imaging¹⁴³. Visual assessment of hypometabolism is less accurate than quantification with a voxel-based comparison with normative data and co-registration with MRI^{144,145}. Absence of unilateral temporal hypometabolism does not preclude a good result from surgery¹⁴⁶. Bilateral temporal hypometabolism was associated with a poor prognosis for seizure remission after surgery¹⁴⁷.

¹⁸F-DG-PET studies have been less reliable for precise localisation of seizure onset than for answering the question of lateralisation. In an evaluation of ¹⁸F-DG-PET in patients with TLE and different pathologies, those with HS had the lowest glucose metabolism in the whole temporal lobe, followed by patients whose seizures arose laterally. Patients with mesiobasal tumours generally had only a slight reduction of glucose uptake in the temporal lobe. The metabolic pattern was different between patients with mesial and lateral temporal seizure onset, but there was not a clear correlation between the location of the epileptogenic focus defined with EEG and the degree of hypometabolism¹⁴⁸. Reduced glucose metabolism and FMZ binding have been reported in the insula in patients with TLE. Emotional symptoms correlated with hypometabolism in the anterior part of the ipsilateral insular cortex, whereas somesthetic symptoms correlated with hypometabolism in the posterior part. Insula hypometabolism, however, did not affect the outcome from temporal lobe resection¹⁴⁹.

Although reduced glucose metabolism may occur in the face of normal structure¹⁵⁰, atrophy is a major determinant of cerebral metabolism measured with ¹⁸F-DG PET, and partial volume correction is necessary to understand the relationship between hippocampal structure and functional abnormalities¹⁵¹. There have been few studies of newly diagnosed patients; only 20% of children with new onset epilepsy had focal hypometabolism¹⁵².

Frontal lobe epilepsy

¹⁸F-DG-PET shows hypometabolism in about 60% of patients with frontal lobe epilepsy. In 90% of those with a hypometabolic area, structural imaging shows a relevant underlying abnormality. The area of reduced metabolism in frontal lobe epilepsy may be much larger than the pathological abnormality. In contrast, however, the hypometabolic area may be restricted to the underlying lesion¹⁵³. There have been three main patterns of hypometabolism described in patients with frontal lobe epilepsy: no abnormality; a discrete focal area of hypometabolism; diffuse widespread hypometabolism. Overall, published clinical series indicate that ¹⁸F-DG-PET does not appear to provide additional clinically useful information in the majority of patients with frontal lobe epilepsy.

Malformations of cortical development

Glucose metabolism has been detected using ¹⁸F-DG-PET in the layers of ectopic neurones in band heterotopia¹⁵⁴ and in heterotopic nodules and displaced grey matter^{155,156}, implying synaptic activity. Cognitive activation tasks using H₂¹⁵O PET, in patients with MCD have shown that heterotopia and malformed cortex may participate in higher cerebral functions, but also showed widespread atypical cortical organisation, indicating that there may be extensive disorganisation of normal structure-function correlates in these patients, that would have implications for the planning of any surgical resection^{157,158}.

In summary, studies with ¹⁸F-DG-PET have defined the major cerebral metabolic associations and consequences of epilepsy but the data are non-specific with regard to aetiology and abnormalities are more widespread than the pathological lesions. The place of the investigation is in the presurgical work up of patients with refractory partial seizures and normal or non-definitive MRI scans, or if data are discordant, in order to generate a hypothesis that may then be tested with intracranial EEG recordings. Activation studies with H₂¹⁵O may determine the functional anatomy of cerebral processes in both healthy and pathological brains; but these studies are now increasingly performed with functional MRI.

POSITRON EMISSION TOMOGRAPHY STUDIES OF SPECIFIC LIGANDS

Positron emission tomography may be used to demonstrate the binding of specific ligands, for example, ¹¹C-flumazenil (FMZ) to the central benzodiazepine-GABA_A receptor complex (cBZR), ¹¹C-diprenorphine and ¹¹C-carfentanil to opiate receptors and ¹¹C-deprenyl to MAO-B. The technique is costly and scarce, but gives quantitative data with superior spatial resolution to SPECT.

Central benzodiazepine receptors

The most important inhibitory transmitter in the central nervous system, gamma amino-butyric acid (GABA) acts at the GABA_A-central benzodiazepine receptor complex. Flumazenil is a specific, reversibly bound antagonist at the alpha subunit types 1,2,3 and 5 of the cBZR and ¹¹C-FMZ is a PET ligand that acts as a useful marker of the GABA_A-cBZR complex *in vivo*.

Comparative studies with ¹⁸F-DG-PET scans have shown the area of reduced ¹¹C-FMZ binding to be more restricted than is the area of reduced glucose metabolism in TLE^{138,139,159-161}. Patients who were seizure free after neocortical resection had smaller non-resected cortex with preoperative FMZ PET abnormalities. In contrast there were no significant correlations between non-resected FDG PET abnormalities and outcome. This implied that abnormalities of FMZ PET indicated epileptic tissue, whereas FDG PET abnormalities were not so predictive¹⁴⁰.

In patients with unilateral HS, reduction of cBZR binding was initially thought to be confined to the sclerotic hippocampus¹⁶². A combination of voxel-based and partial volume corrected regional analyses, however, detected extrahippocampal abnormalities of cBZR binding in 50% patients with HS, and identified bilateral hippocampal abnormalities of cBZR in one-third of patients implying the presence of more widespread abnormalities than previously thought¹⁶³⁻¹⁶⁵.

Quantitative autoradiographic and neuropathological studies of resected HS showed that cBZR density (B_{max}) was reduced in the CA1 subregion of the hippocampus, over and above the loss of receptors that was attributable to neurone loss. In other hippocampal subregions, loss of receptors paralleled loss of neurones and increases in affinity were noted in the subiculum, hilus and dentate gyrus¹⁶⁶. A direct comparison of quantitative *in vivo* hippocampal ¹¹C-FMZ binding and *ex vivo* quantitative ³H-FMZ autoradiographic studies showed a mean 42% reduction of the two measures in patients with HS and a good correlation in individual patients¹⁶⁷.

Utility of ¹¹C-flumazenil PET in the investigation of epilepsy

It seems most likely that cBZR changes reflect localised neuronal and synaptic loss in the epileptogenic zone and that the more extensive hypometabolism is a result of diaschisis. In clinical terms, ¹¹C-FMZ PET may be superior to ¹⁸F-DG for the localisation of the source of the seizure. These data do not confer additional clinically useful information in patients with clear-cut MRI findings of unilateral HS. In a clinical series of 100 patients with partial seizures having pre-surgical evaluation, 94% of those with TLE had an abnormality of ¹¹C-FMZ PET detected, as did 50% of those with other forms of partial epilepsy; 81% of abnormalities found using ¹¹C-FMZ PET were concordant

with abnormalities on MRI. ¹¹C-FMZ PET was useful in the identification of bilateral temporal lobe pathology¹⁶⁸.

¹¹C-FMZ PET is likely to be most useful in conditions in which the epileptogenic area is difficult to define by other means, i.e. patients with focal epilepsy and normal high quality MRI ('MRI-negative') and patients with epilepsy due to malformations of cortical development.

Opioid receptors

Endogenous opioids are released following partial and generalised tonic-clonic seizures and contribute to the post-ictal rise in seizure threshold. Investigations of opioid receptors in patients with TLE have shown an increase of the binding of the specific mu-agonist ¹¹C-carfentanil to mu-receptors in lateral temporal neocortex, reflecting an increase in number of available receptors or increased affinity. It has been speculated that an increase in mu-opioid receptors in the temporal neocortex may be a manifestation of a tonic antiepileptic system that serves to limit the spread of electrical activity from other temporal lobe structures¹⁶⁹.

Dynamic ictal studies of opioid receptors have been carried out in reading epilepsy, using ¹¹C-diprenorphine. In order to localise dynamic changes of opioid neurotransmission associated with partial seizures and higher cognitive function, release of endogenous opioids in patients with reading epilepsy was compared with that in healthy volunteers¹⁷⁰. Reading-induced seizures were associated with reduced ¹¹C-diprenorphine binding to opioid receptors in the left parieto-temporo-occipital cortex and to a lesser extent the left middle temporal gyrus and the posterior parieto-occipital junction. These data gave evidence for localised endogenous opioid peptide release during seizures induced by reading and demonstrate the potential of PET to image release of specific neurotransmitters in response to brain activity in specific cerebral areas *in vivo*.

NMDA receptor

¹¹C-(S)-[N-methyl]ketamine binds to the NMDA receptor, and is thus of interest in studies of epilepsy. In eight patients with medial TLE there was a reduction in tracer binding that paralleled hypometabolism. It is not clear, however, whether the reduction was due to reduced perfusion, loss of tissue or reduction of receptor binding¹⁷¹ and further work is needed to clarify this.

Serotonergic neurones

Alpha-[¹¹C]methyl-L-tryptophan ([¹¹C]AMT) is a marker for serotonin synthesis. In children with tuberous sclerosis, uptake was increased in some tubers that appeared to be the sites of seizure onset. Other tubers showed decreased uptake. In contrast, FDG-PET showed hypometabolism in all tubers. This study suggests that [¹¹C]AMT PET may be useful to detect epileptogenic foci, in patients with tuberous sclerosis, and possibly other forms of cerebral malformation^{172,173}. In 39% of patients with MCD or cryptogenic focal epilepsies there was focal increased uptake of alpha-MT in the epileptogenic area. This may be a further useful tool for localising epileptic foci¹⁷⁴. Increased AMT uptake has been reported to be more specific, but less sensitive for identifying the epileptic focus in children with refractory epilepsy¹⁷⁵, and to be increased in the hippocampus ipsilateral to the focus in TLE¹⁷⁶.

In summary, studies with PET are useful for investigating the neurochemical abnormalities associated with the epilepsies, both static inter-ictal derangements and dynamic changes in ligand-receptor interaction that may occur at the time of seizures. The development of further ligands in the coming years, particularly tracers for excitatory amino acid receptors, subtypes of the opioid receptors and the GABA_B receptor, are necessary to further understand the processes

that give rise to and respond to the various forms of the epilepsies. All functional data needs to be interpreted in the light of the structure of the brain. Coregistration with high quality MRI is essential. It will also be important to carry out parallel studies with *in vitro* autoradiography and quantitative neuropathological studies on surgical specimens and post-mortem material.

Conclusion

There have been significant advances in brain imaging that have revolutionised epilepsy management and particularly surgery. Structural MRI continues to improve and contemporary optimal scans may reveal lesions that were previously not evident. In consequence, rescanning individuals with previously unremarkable MRI is appropriate.

If structural MRI does not indicate a plausible structural cause of the epilepsy, or if a demonstrated lesion is discordant with clinical and EEG data, functional imaging with ¹⁸F-fluorodeoxyglucose PET, and SPECT of ictal-inter-ictal cerebral blood flow can infer the area that contains the epileptic focus and guide intracranial electrode placements. PET with specific ligands is scientifically attractive, but has not had a major impact on epilepsy surgery practice due to limited availability. A recent study assessed the relative predictive value of FDG PET, ictal SPECT and magnetoencephalography against the gold standards of intracranial EEG and outcome of epilepsy surgery. Magnetoencephalography had a high correlation with intracranial EEG, and both PET and ictal SPECT were of additional localising value¹⁷⁷. All three modalities were of benefit in predicting seizure-freedom following surgery¹⁷⁸.

Simultaneous EEG and fMRI can visualise the location of inter-ictal epileptic discharges. These data can assist in deciding on the placement of intracranial electrodes to define the site of seizure onset.

Functional MRI to lateralise language and localise primary motor and somatosensory cortex has entered clinical practice and contributed to the decline of the carotid amytal test. If resections are to be made close to eloquent cortex it is recommended to undertake precise mapping of eloquent function, the site of seizure onset and the irritative zone, to minimise the risk of causing new deficit, and optimise the chance of success. Memory fMRI is less developed, and at present shows promise for predicting the effects of temporal lobe resection in individual patients.

Tractography is used to visualise the major cerebral white matter tracts, and to predict and reduce the risks of surgery. Display of the optic radiation and pyramidal tract are the most relevant for epilepsy surgery at present. The next important step will be reliable integration of all structural and functional data into surgical image-guidance systems so that the data are available real time as surgery progresses.

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CHAPTER 22

Neuropsychology – testing the brain

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Defining and testing cognitive function

Cognitive function is the process by which an individual takes in information about the world, makes sense of it and acts upon it. Neuropsychological tests traditionally assess function in different cognitive domains, all of which can dissociate in the pathological brain. These domains have a conceptual rather than an anatomical basis, although some anatomical correlates do exist. The major cognitive domains include intelligence, language, memory, perception and executive functions. Although we tend to classify our tests under these domains, the majority of neuropsychological tests tap multiple skills from more than one domain. For example, the ability to encode and recall an abstract diagram taps into visual memory but also requires intact perception and adequate comprehension, concentration and praxis. It follows therefore that failure on this test may be the result of a breakdown in any one or more of these processes. The aim of the neuropsychological assessment is not only to identify and quantify deficits in cognitive function, but more importantly to try to identify which processes are breaking down and are therefore responsible for the dysfunction. This is normally achieved by the careful interpretation of an individual's performance and scores on a wide range of tests.

When is neuropsychology useful in epilepsy?

Neuropsychological test results rarely stand alone but are interpreted in relation to both the clinical question being asked (be it a diagnostic issue, the lateralisation or localisation of seizure focus, or the planning of a therapeutic or rehab intervention) and the results from other investigations. There are numerous factors that can influence an individual's performance on neuropsychological tests. Many of these factors are specific to epilepsy and can be fixed, transient or have a progressive influence (Figure 1).

The overall value of a neuropsychological assessment very much depends on the validity of the questions being asked, the condition of the patient on the day and the availability of other relevant data to aid in the accurate interpretation of the test data once it has been collected.

In patients with epilepsy, neuropsychological assessments are most frequently used to aid diagnosis, evaluate the cognitive side effects of antiepileptic medications and monitor the cognitive decline associated with some epileptic disorders. In conjunction with MRI and other presurgical investigations, neuropsychological scores are also used to assess the suitability of patients for epilepsy surgery and can be used to predict post-operative outcome, both in terms of cognitive change and seizure control. The ILAE Diagnostic Commission Neuropsychology Task Force has published guidelines for the indications and expectations for a neuropsychological assessment in both the routine care of people with epilepsy² and in the pre-surgical evaluation and postoperative follow-up of people undergoing epilepsy surgery³.

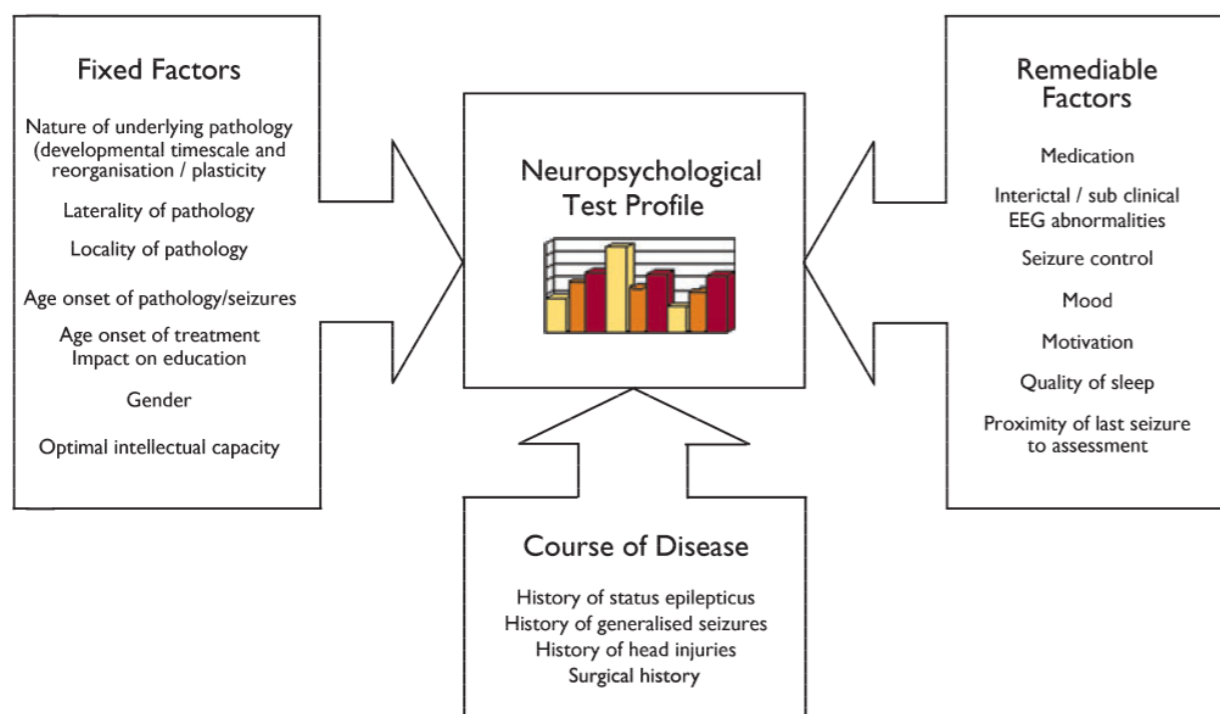


Figure 1. Factors influencing performance on neuropsychological tests in epilepsy. (Adapted from Baxendale and Thompson 2010)¹

In an ideal world, all newly diagnosed patients with epilepsy would undergo a brief neuropsychological screen prior to the onset of treatment to create a valuable baseline against which future assessments can be measured. While resources do not allow such a specialist assessment for most patients, it is possible to have some record of memory function at diagnosis if a self-report questionnaire is administered. The Multifactorial Memory Questionnaire is a freely available questionnaire that has been validated in epilepsy populations⁴⁻⁵.

Serial neuropsychological assessments can be used to evaluate the cognitive side effects of new or existing antiepileptic drug (AED) regimens and to monitor the cognitive deterioration that may be associated with long-term poorly controlled epilepsy and episodes of status. They can also contribute to the diagnostic process. However, repeated assessments over a short period of time can lead to the development of practice effects which can mask a deterioration in function. In most cases it is therefore recommended that there is at least a nine-month interval between assessments to maximise the validity and utility of the results. Single assessments can be useful in the localisation of cognitive dysfunction associated with focal pathologies and also enable the setting of realistic education and employment goals. Single assessments may also reveal deficits that are amenable to rehabilitation.

Neuropsychological tools

General intellectual functioning

The majority of the tests used in the standard neuropsychological assessment remain pencil and paper desktop tasks, though the use of computerised tasks is becoming more widespread. Almost all assessments will include the longstanding gold-standard measure of general intellectual functioning in adults, the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV). The most recent incarnation of the Wechsler Intelligence Scale has dispensed with the traditional distinction

between verbal (VIQ) and performance IQ (PIQ) and now provides four index scores, including the verbal comprehension index (VCI), the perceptual reasoning index (PRI), the perceptual organisation index (POI) and the working memory index (WMI). The full-scale IQ (FSIQ) has been retained and an additional general ability index (GAI) has also been added. The distributions of all the indices are constructed to have a mean of 100 and a standard deviation of 15 IQ points. An index score of 100 therefore defines the performance of an average, healthy, adult at that age. Approximately two-thirds of the adult population obtain scores between 115 and 85, one standard deviation above and below the mean, respectively. Any IQ between 80 and 119 is usually classified as falling within the average range (Table 1).

Table 1. IQ Index Classifications used in the Wechsler Intelligence Scales

IQ Index score ranges	Description	Percentage of the Population who fall within each range
Below 69	Extremely low	2.2
70-79	Borderline	6.7
80-89	Low average	16.1
90-109	Average	50
110-119	High average	16.1
120-129	Superior	6.7
Above 130	Very superior	2.2

Measures of FSIQ may underestimate the intellectual abilities of a significant proportion of people with epilepsy (40%). Reductions in FSIQ are correlated with the number of AEDs taken and duration of epilepsy. Individual AEDs also differentially interfere with the expression of underlying intellectual ability in this group, via their selective actions on processing speed and working memory⁶.

Memory

Memory tests are most frequently divided into three groups: verbal, visual and behavioural memory tasks. The most frequently used verbal memory tests include story recall and list-learning tasks. In these tests the patient is typically read a short local-news type story and asked to recall as much detail as they can immediately after they have heard it and again following a delay of between 30 minutes and an hour. List-learning tasks typically test an individual's ability to learn a list of 15-20 words over a number of trials and frequently include recall and/or recognition conditions following distraction or a delay. Analogous tasks involving non-verbal material include complex figure-recall tasks and design-learning tasks. In the former an individual is required to copy a complex geometric figure and then reproduce as much as they can immediately afterwards and again following a delay of up to an hour. There is a growing consensus that these complex figure-recall tasks may have limited validity in the assessment of epilepsy. Behavioural memory tests are generally thought to be more ecologically valid in that they test 'everyday memory' skills, such as putting a name to a face and prospective memory functions (remembering that you have to do something at some point in the future). Tests are also available to examine retrieval from long-term memory store, including autobiographical recall and memory for public events.

Most neuropsychological assessments will include a screen of expressive and receptive language skills, as well as perceptual abilities. They will also include tests designed to be sensitive to frontal lobe disturbance from both a cognitive and behavioural perspective.

The neuropsychological assessment can be combined with other investigations, such as video telemetry or ambulatory EEG recordings, to investigate the cognitive correlates of interictal EEG discharges or sub-clinical events.

Pre- and post-operative neuropsychological evaluation in epilepsy

Neuropsychological assessment has an important role in evaluating candidates for temporal lobe surgery since the temporal lobes have long been implicated in memory functioning. Bilateral hippocampal excision is associated with profound anterograde amnesia. Unilateral resections are traditionally associated with material-specific memory dysfunction. The traditional view was that the dominant temporal lobe (usually the left) is important for verbal memory processing and the non-dominant temporal lobe (usually the right) for non-verbal or visual memory processing. It is important to recognise that this model of memory function suggests a specialisation of lateralised structures for verbal/visual material rather than an exclusive function. Within this model, the aetiology of the seizure disorder and the underlying pathology may play a critical role in shaping the nature and extent of pre- and post-operative neuropsychological deficits. Different neuropsychological profiles are seen in patients with developmental lesions, such as those associated with cortical dysgenesis, compared to those with high-grade gliomas that develop in adulthood.

Post-operative deficits are dependent upon both the functional adequacy of the tissue removed and the functional reserve of the remaining structures. Some plasticity and the development of compensatory strategies post-operatively may also influence the nature and extent of post-operative neuropsychological deficits. Pre-operative neuropsychological scores, in conjunction with MRI and other clinical data, can be utilised to predict post-operative neuropsychological change using logistic regression techniques. Patients at high risk of a significant memory decline can be counselled pre-operatively and can be trained in compensatory strategies prior to the surgery when appropriate, a process we call pre-habilitation.

The intracarotid amobarbital procedure (Wada Test)

The long running debate on the future of the intracarotid amobarbital procedure (IAP) or Wada test (after Juhn Wada who first introduced it in 1949) and its role in the presurgical assessment of prospective epilepsy surgery candidates is gradually resolving. Traditionally the IAP was used to ensure that the memory capacity of the contralateral temporal lobe is adequate to maintain useful memory functions unilaterally prior to surgery and it is an effective test for language lateralisation. Recent studies have cast doubts on the reliability and validity of the IAP in predicting post-operative amnesia. The testing protocol, choice of behavioural stimuli, dosage and administration of the amytal and a host of factors related to the individual's reaction to the injection can interfere with the results, and many centres no longer conduct Wada tests as part of a presurgical evaluation⁷.

Functional imaging

A number of fMRI paradigms have been developed to localise language function in adults and children and fMRI paradigms have also recently been used to examine memory function in prospective temporal lobectomy patients. Asymmetric fMRI activations during memory tasks are concordant with asymmetric memory performances observed during the IAP. These techniques are superior to the invasive IAP procedure in language lateralisation and are beginning to be combined

with our traditional memory tests to further enhance the role of neuropsychology in providing lateralising and prognostic information for presurgical patients with temporal lobe epilepsy^{8,9}.

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CHAPTER 23

Investigation of seizures in infants

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The investigation of seizures in infancy (i.e. within the first year of life) begins with establishing whether the seizures are epileptic or non-epileptic in origin. The 'broad' differential diagnosis of possible seizures and 'epilepsy' is multiple and is particularly difficult under the age of 12 months and includes:

- Gastro-oesophageal reflux (Sandifer's syndrome)
- Reflex anoxic seizures (pallid syncopal attacks)
- Cyanotic breath-holding attacks
- Cardiac arrhythmias
- Münchausen syndrome by proxy (passive or active - both representing a form of child abuse)
- Shuddering spells and jitteriness
- Hyperekplexia
- Benign neonatal sleep myoclonus
- Benign myoclonus of infancy
- Tonic reflex activity and involuntary movements (seen in children with neurological impairment including cerebral palsy or hydrocephalus).

Once a non-epileptic disorder has been excluded or the episodes are considered to be obviously epileptic, then the following conditions/investigations should be considered on a chronological basis.

Perinatal (first week of life) and neonatal (first month of life) seizures

The newborn period is the time of life with the highest risk of seizures¹⁻³. This is because of the relative lack, and immature development of inhibitory neurotransmitters and their pathways. The immature and developing brain is susceptible to a large number of both cerebral and systemic insults including:

- Asphyxia (hypoxic-ischaemic encephalopathy) - the most common and also most serious cause of neonatal seizures - particularly in term infants
- Intra- and periventricular haemorrhage - particularly in pre-term infants
- Metabolic dysfunction (e.g. hypoglycaemia, hypocalcaemia and hyponatraemia)
- Sepsis (most commonly septicaemia or meningitis but also congenital infections, particularly cytomegalovirus, herpes simplex and HIV-AIDS encephalopathy)
- Cerebral malformation
- Trauma.

The onset of perinatal seizures and timing of the cerebral insult are broadly as follows:

In utero **Day 1** **Day 2** **Day 3** **Day 4** **Day 5** **Day 6 (and beyond)**

Cerebral malformation/dysgenesis ----->
 Intrauterine (congenital) infection ----->
 Pyridoxine/pyridoxamine dependency/deficiency ----->

Perinatal asphyxia
 Sepsis
 Hypoglycaemia
 Maternal drug withdrawal
 Periventricular haemorrhage

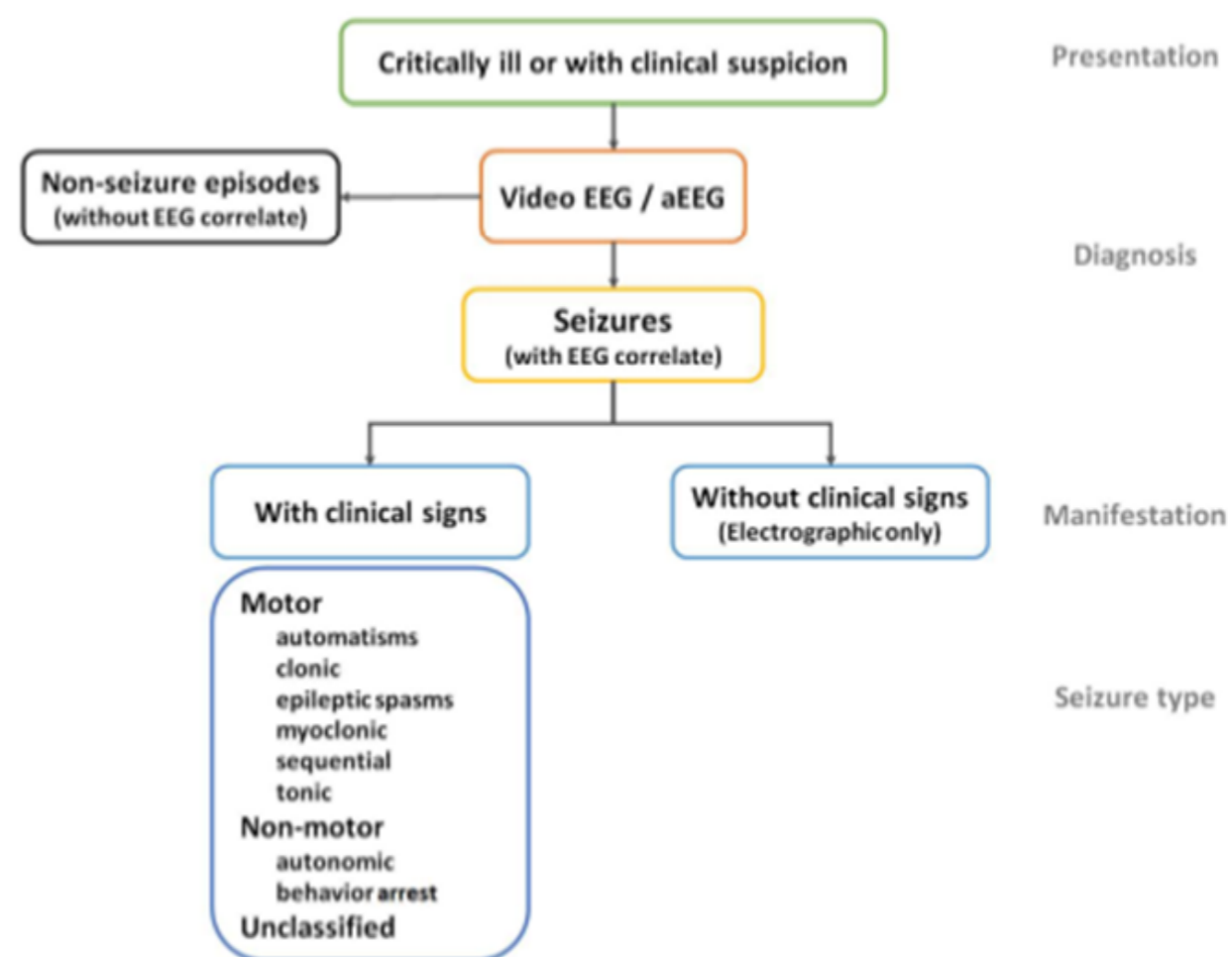
Hypocalcaemia
 Benign familial neonatal convulsions

Aminoacidopathies
 Galactosaemia
 Ketotic and non-ketotic hyperglycinaemia
 Early infantile epileptic encephalopathy
 Folinic acid-responsive neonatal seizures
 Glucose transport protein deficiency

Migrating partial seizures (epilepsy) of infancy

Perinatal and neonatal seizures are both over- and under-diagnosed. Classifying events as epileptic or non-epileptic can be particularly challenging in the neonatal period due to the immaturity of the motor pathways of preterm and term infants and the complexity of their clinical state especially in the neonatal intensive care unit. Seizures in the neonatal period have been classified as clinical only, electric-clinical and electrographic. It is not clear whether all clinical only seizures are epileptic in origin. Generalised tonic-clonic seizures do not occur in neonates, and most seizures are myoclonic or clonic and focal and fragmentary, again reflecting an immature brain. The ILAE task force on neonatal seizures have drafted a proposed new classification for seizures in the neonatal period which is available on ILAE classification website (<https://www.ilae.org/guidelines/definition-and-classification/neonatal-seizure-classification>).

Classification of events in neonatal period is crucial and the use of video-EEG is the gold standard as not all abnormal movements (particularly in premature babies) are seizures and clinical differentiation of seizure from non-seizure activity may be very difficult. Where video-EEG is not available then amplitude integrated EEG (cerebral function monitoring) can be helpful to assess for electrographic events and correlate clinical manifestations with any electrical change.



Proposed diagnostic framework of seizures in the neonatal period including classification of seizures. Adapted from 2017 ILAE seizure classification.

The aetiologies of neonatal seizures are multiple. In most cases the underlying aetiology can be determined from preceding events, the clinical course (including the pregnancy), family history and physical examination. If there is no definite history of perinatal asphyxia, an initial 'screen' should be undertaken:

- Blood glucose, calcium, magnesium, urea, electrolytes and acid-base status
- Full blood count and film examination
- CSF analysis (glucose [with a simultaneous fasting blood glucose], protein, cell count)
- Cultures of blood, CSF, urine and faeces
- Cranial ultrasonography (only of use when looking for evidence of haemorrhage or a *major* cerebral malformation).

Further investigations should be performed depending upon the clinical situation and results of the initial evaluations:

- Blood ammonia, lactate, uric acid and liver enzymes; biotinidase level; if the blood creatinine level is consistently low, further more detailed biochemical and genetic analyses should be undertaken looking for evidence of abnormalities of creatine synthesis (e.g. GAMT deficiency)
- Blood and urine amino acids, urinary organic acids
- Urine-reducing substances; urine sulphite levels
- 'TORCH' antibody studies (for congenital infections)
- MRI head (for cerebral malformations)
- Diagnostic use of pyridoxine (vitamin B6) and/or pyridoxal-5-phosphate
- CSF analysis (glucose, lactate, amino acids)
- Chromosome and DNA analysis. There are an increasing number of gene abnormalities associated with infantile epilepsies. Some of these can now be detected on infantile epilepsy gene panels - discuss with genetics team.

The condition of pyridoxine-dependent seizures is a rare autosomal recessive disorder that presents characteristically within the first week of life with intractable seizures and a markedly abnormal (almost hypsarrhythmic-like, often with a burst-suppression pattern) EEG⁴. However, it may also 'present' before birth with intrauterine seizures, or late, even up to 12 or 18 months of age. Clinical response to intravenous pyridoxine (vitamin B6) is often immediate as is normalisation of the EEG, although the latter may be delayed for days or weeks. Therefore a trial of oral pyridoxine (20–30 mg/kg/day) should be given for at least three weeks. Some infants have an abnormality further down the metabolic pathway and require treatment with pyridoxal-5-phosphate as pyridoxine will not be effective in these infants. Some clinicians would recommend using pyridoxal-5-phosphate instead of pyridoxine to ensure that all infants who have a defect in this metabolic pathway will be treated in an appropriate manner⁶. Also, it is recommended that any infant under the age of 18 months with intractable seizures of unknown cause should receive a similar trial of pyridoxine. A biochemical marker (elevated levels of pipercolic acid in plasma, urine and/or CSF) and mutations in ALDH7A1 gene have recently been identified in a number of infants with pyridoxine-dependent seizures and provide a definitive diagnosis of this rare syndrome⁷ which was previously diagnosed by a 'therapeutic challenge' of pyridoxine.

The treatment of perinatal and neonatal seizures depends largely on the aetiology. Any underlying cause such as drug withdrawal, electrolyte disturbance or a treatable metabolic disorder (including hypoglycaemia and hypocalcaemia), should be corrected. Antiepileptic drug (AED) treatment is virtually always indicated if a correctable metabolic cause is not identified; pyridoxine/pyridoxal-5-phosphate should be given early if seizures are resistant to conventional AED therapy and biotin also given, pending the result of a serum biotinidase level. Phenobarbitone is used as the usual first-line drug, but ideally only in the acute situation where early seizure-control is required.

Levetiracetam, lidocaine and midazolam are other useful drugs, often given as infusions (rather than as boluses) in 'refractory' neonatal status epilepticus. If seizures persist the infant **must** be discussed with a paediatric neurologist as rare conditions, including a mitochondrial cytopathy,

glucose transport protein deficiency, carbohydrate deficient glycoprotein syndrome, sulphite oxidase deficiency or folinic acid-responsive seizures, must be considered and either confirmed or excluded by the relevant investigations.

Most neonatal seizures are acute symptomatic in origin with the seizures tending to resolve, usually spontaneously. In this situation it would be reasonable to withdraw medication four or at most six weeks after the 'symptomatic' insult (assuming the infant is seizure free) – and to restart an AED if seizures then recurred. The drug of choice then would be dependent upon the seizure type (or types), and the overall neurological/developmental status of the child. Drugs of first choice would include carbamazepine (focal seizures), sodium valproate (myoclonic, atonic or generalised tonic-clonic/clonic seizures), and steroids (infantile spasms); phenobarbitone would not be drug of first choice for treating 'late' epilepsy i.e. out with neonatal period. Sodium valproate should be avoided in any infant with frequent myoclonic seizures, in whom the cause of the seizures is as yet unknown, or if there is any suspicion that the infant may have an underlying metabolic disorder and specifically a mitochondrial cytopathy.

A number of outstanding issues remain to be answered regarding neonatal seizures:

- There are inadequate data indicating whether neonatal seizures produce cerebral damage or are completely 'harmless'. There is some circumstantial evidence that neonatal seizures increase the risk of later epilepsy and, possibly, cognitive impairment in children who subsequently develop cerebral palsy (CP)⁸. However, it is likely that the aetiology of the seizures is more important than the seizures themselves.
- There is almost no information on the effects of AEDs on the developing brain.
- Many pharmacokinetic properties of AEDs (particularly phenytoin) are unique to the neonatal period and may result in problems of both drug efficacy and toxicity.
- The value of AED treatment beyond the neonatal period to prevent later epilepsy is unknown.

Epilepsy Syndromes in Neonates and Infants

Self-limited familial Neonatal Seizures⁹

As already stated, this syndrome may present in the newborn period (characteristically in the first week of life), and is rarely seen after eight weeks of age. Seizures are usually hemiclonic and can involve some autonomic features and may become bilateral. There is no known cause for this condition, but it is believed to be inherited with autosomal dominant inheritance and at least two genes have been identified - one on chromosome 20q (KCNQ2) and one on 8q (KCNQ3, less common than KCNQ2 mutations). Neurological and developmental outcome is normal, but approximately 10–12% of these infants develop later epilepsy (in adolescence or in early adult life), usually generalised tonic-clonic seizures. In most infants, seizures resolve between six weeks and six months of age. The precise incidence (and prevalence) of this syndrome is unknown. The inter-ictal EEG is usually normal.

Self-limited (non-familial) neonatal seizures⁹

This is another rare type of neonatal convulsions which has very similar clinical and electrical features to the familial form above. It may be that some neonates with this condition have a de novo genetic mutation, and therefore there is no family history. It is likely that this represents the entity known previously as 'fifth day fits', which was once considered (entirely erroneously), to be due to zinc deficiency. Seizures may persist for longer than in the familial form but late epilepsy is much less common (under 1%), and may have no causal relationship.

Epilepsy of infancy with migrating focal seizures (migrating partial seizures in infancy^{10,11})

Although this would appear to be a rare syndrome it is probably under-recognised, like most new epilepsy 'syndromes'. Most infants present at less than six months of age and the majority at less than six weeks of age. The seizures are brief but multiple and at their peak may occur over 50 or 60 times per day. Eye and/or head deviation, autonomic features (facial flushing and epiphora) and some facial/limb clonic activity characterize the seizures. As the name implies, the seizures originate from (and migrate to) different parts of the brain – both clinically and electrically, in the EEG. Developmental progress is generally very poor (from the onset of the seizures) and survivors usually have moderate or severe learning difficulties. Many infants die under two or three years of age. There is emerging evidence of a genetic aetiology to this disorder with mutations in KCNT1 being the most frequently reported but also cases with SLC25A22, SCN1A, SCN2A, TBC1D24, SCN8A and CHD2 mutations. Seizure-control is usually very poor and no one anticonvulsant has proved to be any more effective than another. Ketogenic diet and vagal nerve stimulation also are generally ineffective. There has been some recent interest in gene-targeted treatment in children with KCNT1 mutations using quinidine, however further evaluation of this is required¹².

Myoclonic epilepsy in infants

Early onset, severe (early myoclonic encephalopathy) (EME). The condition may be independent from, or, far less likely, may overlap with Ohtahara syndrome¹³ (early infantile epileptic encephalopathy with burst-suppression on EEG). Both syndromes are severe epileptic encephalopathies with a poor prognosis; seizures are typically resistant to treatment, psychomotor retardation is both inevitable and profound and life expectancy is limited. In EME seizures typically start in the first two months of life (with the majority starting in the first ten days) and myoclonic seizures are frequent (distinguishing the condition from Ohtahara syndrome). Metabolic aetiologies are common (non-ketotic hyperglycaemia is the commonest metabolic aetiology, and amino and organic acidopathies, urea cycle disorders, mitochondrial disorders, pyridoxine and pyridoxal-5-phosphate disorders, molybdenum cofactor deficiency, sulfite oxidase deficiency, Menke syndrome, Zellweger syndrome and other disorders are also seen) and structural abnormalities are rare. A number of familial cases have been reported raising the possibility of a genetic aetiology. Gene mutations have been reported in several different genes in infants with EME, including ErbB4, SLC25A22, SIK1 and GABRB2.

Treatable metabolic aetiologies should be investigated at presentation and all infants should have a trial of pyridoxal phosphate. AEDs are generally ineffective and ketogenic diet has not been particularly beneficial in this condition.

Late-onset, severe. Dravet syndrome (previously known as severe myoclonic epilepsy of infancy, SMEI) is a rare syndrome with an estimated frequency of one in 20,000-40,000¹⁵. Otherwise normal infants develop generalised or focal myoclonic seizures in the first few weeks or months of life, sometimes following vaccinations; rarely the onset may be as early as the first week. Infants far more commonly present at 6-9 months of age with isolated but prolonged and often focal 'febrile seizures' or febrile status epilepticus. Myoclonic, tonic-clonic and focal seizures then develop, often explosively, in the second or third year of life. The child's development may stagnate and may even regress, particularly in receptive and expressive speech and language skills. Around 70-80% of patients with Dravet Syndrome have a mutation in the alpha (α) subunit of the first neuronal sodium channel gene (SCN1A) on chromosome(s) 19 and/or 2 (95% de novo; 5% inherited). Sodium valproate, clobazam and stiripentol are often used in combination in treating this syndrome. Topiramate, levetiracetam and the ketogenic diet have also been reported to be helpful. Importantly, lamotrigine and carbamazepine, even in relatively low doses, may significantly exacerbate the myoclonic seizures – and this observation is often used as a clue in establishing a diagnosis of Dravet Syndrome.

There has been recent interest in the use of cannabidiol (CBD) in Dravet syndrome, and a RCT¹⁷ has shown 43% of patients randomised to CBD had a ≥50% reduction in convulsive seizures compared to 27% of patients taking placebo. CBD was associated with significantly higher rates of adverse events, including diarrhoea and somnolence. CBD is only available in the UK currently though an early access programme as it does not yet have authorisation from European Medicines Agency, though a submission has been made and is being evaluated.

Fenfluramine has been shown to be beneficial in reducing epileptic seizures in Dravet syndrome in small open label studies. A RCT is currently underway to evaluate the safety and efficacy of this drug in Dravet Syndrome.

Myoclonic epilepsy in infancy (self-limited). Myoclonic epilepsy in infancy (previously known as benign myoclonic epilepsy in infancy) is characterised by brief episodes of generalised myoclonic seizures which may commence in the first (or more commonly in the second) year of life in otherwise normal children who frequently have a family history of epilepsy or febrile seizures. The myoclonic seizures are brief, may be massive and can occur on or soon after falling asleep or with stimulation (noise or touch). The only relevant investigation is the EEG, which shows generalised spike-wave or polyspikes occurring in brief bursts during the early stages of sleep, and 20% have photosensitivity. Valproate readily controls the infantile myoclonus. Levetiracetam may be a useful alternative. While it is considered most likely to have a genetic basis, no genes have been identified to date. In most children, seizures either remit spontaneously or are relatively easily controlled with AEDs. Febrile seizures occur in about 10% and generalised tonic-clonic seizures may develop in adolescence.

Ohtahara syndrome

Ohtahara syndrome presents in the first three months of life and is a severe epileptic encephalopathy. It can be distinguished from EME due to the predominance of tonic seizures and the relative infrequency of myoclonic seizures. However, like EME it has a poor prognosis with a drug-resistant epilepsy, severe psychomotor retardation and limited life expectancy. Structural brain abnormalities are the commonest cause of this epilepsy syndrome (e.g. hemimegalencephaly, porencephaly, Aicardi syndrome, olivary-dentate dysplasia, cerebral dysgenesis and focal cortical dysplasia) but genetic mutations (STXBP1 [10-15% of cases], SLC25A22, CDKL5, ARX, SPTAN1, PCDH19, KCNQ2, and SCN2A) are being increasingly reported. Metabolic aetiologies also occur (mitochondrial disorders, non-ketotic hyperglycaemia, pyridoxine/pyridoxal-5-phosphate disorders, carnitine palmitoyl transferase deficiency, and biotinidase deficiency).

In terms of treatment AEDs are often not effective. Sodium valproate, phenobarbitone, vigabatrin, benzodiazepines and zonisamide have all demonstrated some limited effectiveness, as has the ketogenic diet. Treatable metabolic disorders should be identified early as appropriate treatments are of clinical benefit. Children with focal structural brain malformations should be referred to an epilepsy surgery programme as epilepsy surgery may be effective in terms of both seizure control and neuro- developmental outcome.

Prognosis is poor in this condition with 25% of children dying in infancy. Many infants with Ohtahara syndrome will evolve into West Syndrome during infancy.

West syndrome^{18,19}

This syndrome is one of the most severe that occurs in the first year of life with typical age of onset between 3 and 10 months (peak 6-8 months). The full syndrome comprises an electroclinical triad, although only the first two features are required to diagnose the syndrome:

- Epileptic spasms (flexor and extensor seizures occurring typically in clusters, with between five and 50 per cluster usually on or soon after waking).
- Hypsarrhythmia on the EEG (though this is not present in all infants with West syndrome at presentation and may be demonstrated only in sleep).
- Developmental delay (not invariable at the onset of the spasms and therefore not essential for the diagnosis of the syndrome).

Approximately 80% have an identified aetiology. Common causes include:

- Structural brain disorders
- Malformations of cortical development (e.g. lissencephaly, cortical dysplasia)
- Neurocutaneous syndromes (tuberous sclerosis, incontinentia pigmenti, neurofibromatosis)
- Acquired brain injury (e.g. a sequel to hypoxic-ischaemic (perinatal asphyxia) encephalopathy, post- meningoencephalitis)
- Metabolic disorders (e.g. biotinidase deficiency, Menke's disease, phenylketonuria, non-ketotic hyperglycinaemia, mitochondrial cytopathy)
- Chromosomal disorders (Down syndrome, Miller-Dieker syndrome)
- Genetic causes (ARX, CDKL5, SPTAN1, STXBPI).

There are however many other causes.

The remaining 20% have no obvious cause. Almost certainly this number will fall over the forthcoming years with further advances in functional neuroimaging (MRI, tractography and magnetoencephalography [MEG]), molecular genetics and biochemistry.

The investigation of infantile spasms depends largely on the individual child and its previous medical (particularly perinatal) history. All infants require imaging with MRI. A negative (normal) CT should never be regarded as excluding a structural lesion.

First-line treatments for West syndrome are ACTH (tetracosactide), prednisolone and vigabatrin^{20,21}. ACTH/prednisolone is more effective than vigabatrin in controlling spasms early on (at 14 days), but is similar in efficacy in long-term follow-up (12–14 months)²². Vigabatrin appears to be particularly effective for infants who have West syndrome caused by tuberous sclerosis. A study evaluating the use of combination treatment with ACTH/prednisolone and vigabatrin compared to ACTH/prednisolone alone (the ICISS – International Collaborative Infantile Spasms Study) has reported that combination therapy of hormonal therapy and vigabatrin is associated with a more rapid clinical response and greater proportion of infants achieving spasm cessation than on hormonal therapy alone²³, but did not result in improved developmental or epilepsy outcomes at 18 months²⁴.

Other treatments that are of benefit in West Syndrome include nitrazepam (which in a historic comparator trial has been shown to have similar efficacy to ACTH, but fewer side effects²⁵), sodium valproate, topiramate, levetiracetam, zonisamide and pyridoxine. The ketogenic diet should be considered in infants with West syndrome which is resistant to medication. Children who have

focal structural abnormalities and drug-resistant spasms should be referred to an epilepsy surgery centre to consider whether they are suitable candidates for resective epilepsy surgery.

Febrile seizures²⁶

Defined as 'convulsions with fever in children aged between six months and five years without evidence of serious acute symptomatic brain disease (e.g. meningitis, encephalitis)' (see also Chapter 8). Although by *definition* children as young as six months of age may have febrile seizures, it would be appropriate to consider and investigate for the following disorders in children less than one year:

- Meningitis/encephalitis
- Metabolic disorder
- Malformations of cortical development.

Clearly the number and type of investigations undertaken would depend upon the age of the infant and whether the febrile seizure was 'simple' or 'complex' (complex means a seizure which is focal, serial, longer than 15 minutes, or followed by a neurological deficit). For example, a complex febrile seizure in a six-month-old infant should at least raise the possibility that the child may be developing Dravet Syndrome (described above) and would justify at *least* the exclusion of meningitis by CSF analysis and urine culture. It would also merit neuroimaging (preferably MRI) to exclude or demonstrate a structural lesion (including malformations of cortical development). If these investigations are negative it would be appropriate to screen for SCN1A mutations. A simple febrile seizure in a one-year-old with no obvious focus of infection would justify CSF and urine analysis however. A simple febrile seizure in a two or three-year-old child with otitis media probably needs no investigation and specifically there is no indication for undertaking an EEG in this situation.

Frequently a complicated febrile seizure may actually represent a first epileptic seizure that has been provoked by an intercurrent infection. Over the past few years, there has been the identification of a 'syndrome' of generalised epilepsy and febrile seizures plus (GEFS+) which may present with febrile seizures in the first two years of life. The word, 'plus' in this syndrome refers both to the fact that febrile seizures may still occur after the age of five years *and* that other afebrile seizures (of multiple types) may occur in later childhood or adult life. Mutations in a number of genes^{27,28} have been associated with this disorder including SCN1A, SCN1B, GABRG2 and PCDH19.

Summary and conclusions

- Although the newborn period is the time of life when epileptic seizures occur most commonly, firstly not all involuntary including 'jerky' or 'twitchy' movements are epileptic and secondly, most causes of genuine epileptic seizures are secondary to (or symptomatic of), an underlying cause. If in doubt that the movements or other paroxysmal events (e.g. autonomic changes) are epileptic – do not diagnose epilepsy and investigate with video-EEG
- There are a relatively large number of epilepsy syndromes that have an onset in infancy (the first year of life) and most are associated with a poor prognosis, both in terms of seizure control and eventual spontaneous remission but also development and cognitive functioning
- Never overlook a simple biochemical or metabolic cause of seizures in neonates and infants (specifically, glucose, calcium and sodium)

- Cranial ultrasound and skull radiographs are of little diagnostic value when evaluating the cause of an infant's seizures. MRI is the imaging modality of choice – particularly when considering malformations of cortical development as a cause of the epilepsy
- Genetic investigations, such as the Rett syndrome mutations (MECP2 and CDKL5) should be considered early when confronted with a child with intractable seizures and no obvious cause; infantile gene panels using next-generation sequencing of increasing numbers of known genes are now readily available and whole exome/genome studies are likely to become available for clinical use soon
- Avoid polypharmacy (the simultaneous use of more than two AEDs) in treating seizures in infancy. When about to add another AED, always try and withdraw another one first or simultaneously – though this is always easier said than done!

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CHAPTER 24

Investigation of progressive neurological impairment in children with epilepsy

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When a child presents with epilepsy and developmental/cognitive stagnation or decline, the question of whether this could be an initial feature of a progressive neurodegenerative disease should be considered. Epilepsy as a sole presenting feature of a neurodegenerative condition is rare, but recognised in a certain number of disorders (see below). One must also consider whether the cognitive decline is secondary/related to the epilepsy.

Cognitive or developmental plateau or regression is well recognised at the onset of certain of the more severe early epilepsy syndromes. The underlying pathophysiology to this remains uncertain, however, and appears to be related in part to the early onset of frequent seizures. The term 'epileptic encephalopathy' is recognised as part of the ILAE classification of the epilepsies¹, described as disturbances of cognition, behaviour, and motor control that occur with epileptic seizures and are attributed to epileptiform activity, which may be subclinical. Many individuals show periods of apparent improved developmental progress in association with improved seizure control. In some children it is relatively easy to determine the relationship of epilepsy to the cognitive problems and the need to investigate such. Although aggressive treatment of overt seizures is appropriate, it is more difficult to define the criteria to treat subclinical discharges, in the absence of overt non-convulsive status epilepticus.

Is it real?

The initial phase of the evaluation is to determine whether the cognitive decline is 'real' as opposed to 'apparent'. Children may experience developmental plateau in association with the presentation of severe epilepsy. There is usually an accurate documentation by the parents of previous developmental milestones, and the history may give detail of lack of progress with, rather than loss of, milestones. In some children with long-standing epilepsy lack of progress becomes evident. In these children, learning does not progress with age, which means the gap between the child and their peers widens – with a consequent drop in IQ. This is not a loss of skills but rather a failure to progress, and becomes particularly apparent around the age of seven years when abilities such as practical reasoning and abstract thought start to develop in normal children.

Key points in the history are age at onset, the relationship or not to frequency of seizures, and the pattern of regression. A pattern of fluctuating abilities as opposed to steady decline is likely to suggest an epileptiform basis, although some neurodegenerative conditions may show a stepwise progression. Periods of apparent encephalopathy should also alert the doctor to the need for investigation. The history may distinguish whether this is likely to be part of a metabolic disorder or periods of non-convulsive status, but investigation at the time of acute deterioration may be the only way to differentiate between these.

The emergence of neurological signs in a child with epilepsy, in association with possible cognitive decline, signals the need for investigation, particularly if signs are progressive. These include a motor disorder with pyramidal or extrapyramidal signs and abnormalities of eye movement. There remains the possibility that this is still epileptiform in origin; motor disorders such as monoparesis or ataxia may revert with aggressive antiepileptic drug (AED) treatment. However this does not preclude the need for exclusion of other causes, as the EEG itself may be inconclusive. It is also unusual for epilepsy alone to present with hard neurological findings on examination unless a known deficit has been previously established.

Epileptiform or non-epileptiform?

The mechanisms of cognitive/neurodevelopmental plateau or regression in certain epileptic encephalopathies remain unclear. Early-onset epilepsy syndromes are particularly associated with plateau/regression of neurodevelopment and this is invariably seen in early myoclonic encephalopathies, West syndrome, Dravet syndrome and the Lennox-Gastaut syndrome.

West syndrome pertains to the triad of infantile spasms, hypsarrhythmia on the EEG, and developmental plateau. The latter involves a regression in communication skills with poor eye-to-eye interaction. Infantile spasms may occur in association with a variety of pathologies, although the EEG and developmental pattern may be similar. Prognosis with regard to initial seizure control is relatively good with (sometimes given in combination with vigabatrin), however it remains poor with regard to developmental outcome, and the later development of further seizures. Developmental outcome appears better in some infants who are treated early after presentation and in whom there is a rapid resolution of seizures and EEG abnormality, suggesting that the epileptic activity plays a major part in subsequent cognitive development. However the underlying pathology is a strong indicator of future developmental outcome.

Some conditions associated with focal epilepsy can also feature a similar clinical picture of neurodevelopmental regression at presentation. For example, Sturge-Weber syndrome is characterised by a facial capillary haemangioma (port wine stain) involving the periorbital area, forehead or scalp, a venous angioma of the leptomeninges and, in a proportion of cases, a choroidal angioma. Epilepsy is reported in approximately 80% cases. However, these figures are derived from selected groups of individuals with Sturge-Weber syndrome, and may therefore not be fully representative of all cases. Seizures start in the first year of life in the majority. One study found that the onset of epilepsy was within the first two years of life in 86%, and 95% by five years of age. Early-onset, poorly controlled seizures, sometimes with episodes of status epilepticus, tend to be associated with progressive hemiparesis and developmental slowing; in such cases early resective surgery should be considered. The underlying pathophysiology of the 'encephalopathy' is unclear, but may be related to ischaemia secondary to venous hypertension within the angioma.

Landau-Kleffner syndrome is an age-related syndrome with a probable focal aetiology leading to a more widespread encephalopathy. Typically, children have a period of normal language development, followed by a period of language regression with auditory agnosia. There is a marked associated behaviour disorder. Seizures may be infrequent, but a profound abnormality is seen on the EEG, usually over the temporal regions. Some may demonstrate very little in the waking state, however, but show almost continuous spike-wave activity in sleep (electrical status epilepticus in slow sleep/continuous spike-wave in slow sleep). Although conventional AEDs may have some benefit, there appears to be a particular role for steroids early in the treatment of this disorder, in an attempt to reverse the language disorder.

It is becoming increasingly evident that a progressive epileptic encephalopathy may be seen in association with certain chromosomal abnormalities, most notably ring chromosome 20. These

children present with an early onset apparent focal (frontal) epilepsy. Onset is usually before six years of age. Seizures are often bizarre in semiology, although suggestive of frontal origin; they may include seizures with fear, often with visual symptoms, hallucinations and illusions, generalised tonic-clonic or tonic-clonic seizures, nocturnal tonic seizures or arousals and recurrent non-convulsive status epilepticus. Cognitive outcome is variable although a plateau in skills not inevitable.

To what degree is autistic spectrum disorder related to epileptic regression?

The cognitive plateau and regression seen in association with some of the early epileptic encephalopathies may show a particular pattern, particularly involving communication skills, with similarities to children presenting with autistic spectrum disorders (ASD). This is seen in children with infantile spasms, and also in children with early presentation of seizures associated with right temporal lobe lesions, especially boys. Conversely, a number of children with classical presentation of ASD have epileptiform abnormalities on EEG (30%) and up to 20% have epilepsy. The question arises as to how much of the epileptiform activity seen on EEG, particularly in sleep, is related to the autistic regression, and how much this warrants aggressive AED treatment. To date, there are no studies demonstrating the relationship of epileptiform abnormalities on EEG to ASD, or the merits of treatment. Most children showing a response are those who present with a history of some seizures, and therefore warrant investigation and treatment from this standpoint. The potential role of AEDs in others needs further investigation but at the moment there is no evidence base to support treating epileptiform abnormalities on the EEG of children with ASD.

Epilepsy as the presentation of a neurodegenerative disorder

A few conditions have epilepsy as a presenting feature (Table 1). The range of disorders that need to be considered will depend on the age at presentation. In the neonate, metabolic disorders, particularly non-ketotic hyperglycaemia, may present with a clinical/electrophysiological picture suggestive of hypoxic ischaemic encephalopathy, with very early seizures and a burst-suppression picture on EEG. One may be alerted by the apparent lack of history of a significant hypoxic insult. Later in the first year, Menkes disease and biotinidase deficiency may be suggested by the condition of the hair.

Alpers' disease (also known as progressive neuronal degeneration of childhood – PNDC) is a rare but well recognised disorder in which progressive epilepsy is seen in association with liver dysfunction. The condition usually presents in the first two years of life, though may present at any time during childhood and even into early adult life. It is an autosomal recessive disease caused by mutation in the gene for the mitochondrial DNA polymerase POLG. It is likely that many of the historically reported valproate-associated hepatic failures occurred in individuals with Alpers' disease.

Late infantile neuronal ceroid lipofuscinosis (Batten disease) presents with initial seizures in the second year of life, usually including myoclonus with a subtle developmental plateau that may only later become apparent as regression. Electrical visual studies may lead to suspicion (with enhanced visual evoked response), and confirmation with white cell enzyme analysis and genetic studies.

In older children, conditions that may still need to be considered include subacute sclerosing panencephalitis (SSPE). Progressive behaviour change in association with periodic jerks will give a clue to this. Wilson's disease may have associated movement disorder and behaviour change, with Kayser Fleischer rings on the iris. Extrapyramidal features, in particular in association with non-epileptic drop attacks (cataplexy) may suggest Niemann Pick type C.

The progressive myoclonic epilepsies are again likely to present with infrequent seizures, with a later increase in frequency and associated cognitive concerns. A high index of suspicion is required to investigate these early.

Table 1. Neurodegenerative conditions that may present with epilepsy as a symptom.

Infancy	1-5 years	5-10 years	Adolescence and adulthood
Metabolic	Mitochondrial cytopathy	SSPE	Progressive myoclonic epilepsy
• Non-ketotic hyperglycinaemia	Homocysteinuria	HIV	• Lafora body
• D-glyceric aciduria	Rett syndrome	Alpers' disease	• Unverricht-Lundberg
• Hyperammonaemia			Sialidoses
Biotinidase deficiency	Late infantile NCL	Wilson's disease	Alpers' disease
Late infantile NCL	Gauchers type III	Niemann Pick type C	
Menkes syndrome	Alpers' disease		
Krabbe disease			
Tay Sachs disease			
Peroxisomal disorders			
Alpers' disease			

NCL: neuronal ceroid lipofuscinosis; SSPE: subacute sclerosing panencephalitis; HIV: human immuno-deficiency virus

Table 2. Investigations to consider with 'true' neurological deterioration in association with epilepsy.

EEG (including sleep)
ERG/VEP
MRI
Blood
• FBC, LFT, NH ₃ , amino acids, lysosomal enzymes, VLCFA, bile salts, vacuolated lymphocytes/buffy coat, Cu/Caeruloplasmin, biotinidase, lactate
Genetic studies for specific conditions
• Discuss with paediatric neurologist and geneticist
Urine
• Amino acids, organic acids
CSF
• Lactate, amino acids, virology
Biopsy
• Skin, liver, muscle

EEG: electroencephalogram; ERG: electroretinogram; VEP: visual evoked potential; FBC: full blood counts; LFT: liver function tests; VLCFA: very long chain fatty acids

What investigation when?

Recognising the need for investigation and deciding which investigations to consider is often the most difficult task. Investigations that may be considered are outlined in Table 2.

Obviously, some are highly specific and more invasive, and a high index of clinical suspicion is therefore required to direct the investigation required. Discussion with metabolic team and input from other specialities e.g. ophthalmology may be helpful in deciding which investigations are most relevant. Recognising that intrinsic pathology is present may be difficult in the early stages of presentation of many disorders, and constant re-evaluation of the individual may be necessary.

Summary and Conclusions

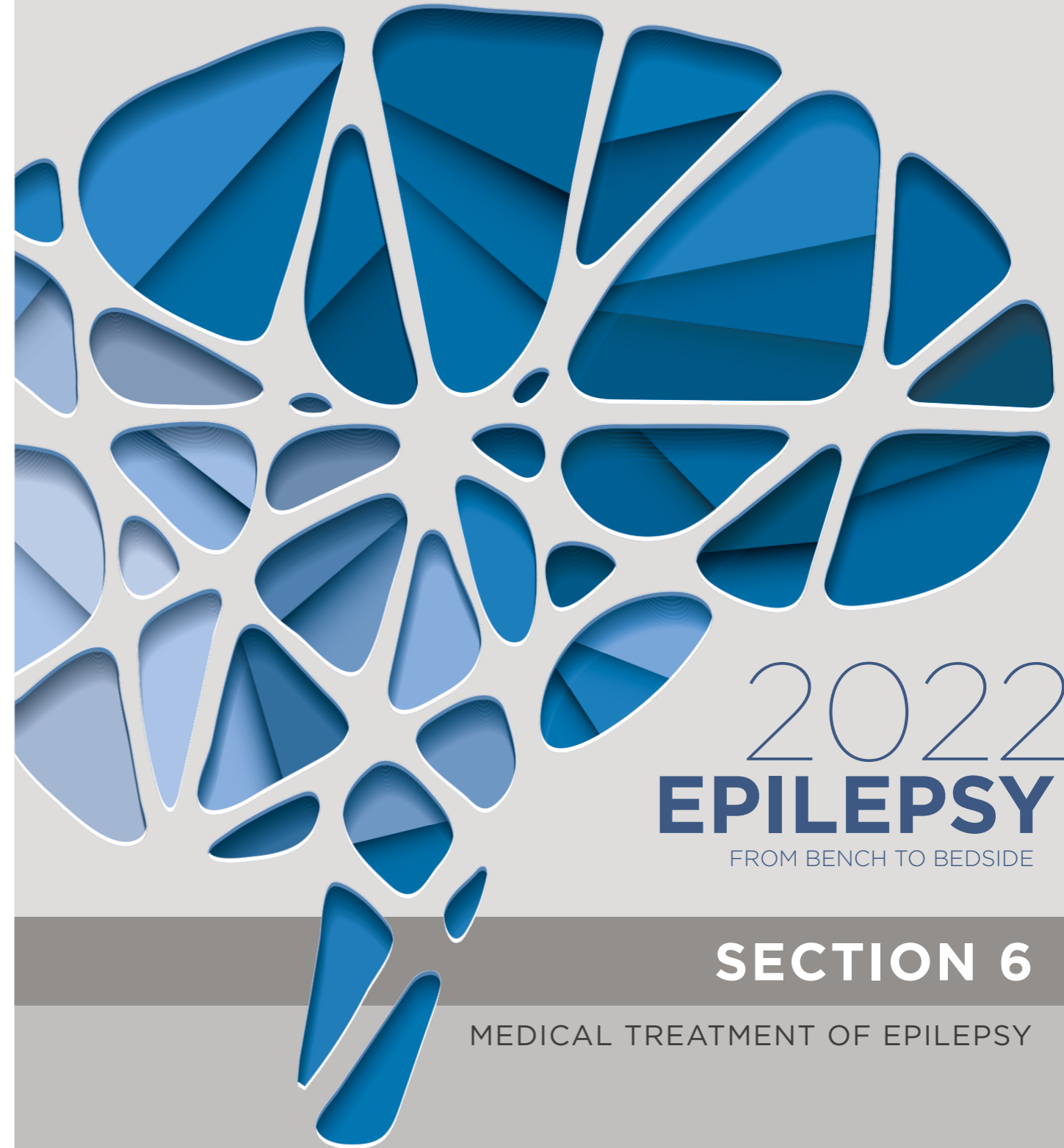
- Epilepsy as the sole presentation of a neurodegenerative disease is rare, but if occurs with developmental/cognitive stagnation or regression and particularly if new neurological signs appear a neurodegenerative condition should be considered
- It is important to establish whether developmental/cognitive decline or regression in children is associated with an epileptic encephalopathy and to identify and treat this
- There is an extensive range of investigations for neurodegenerative conditions and the choice of investigations should be guided by age of presentation and clinical features

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 6

MEDICAL TREATMENT OF EPILEPSY

CHAPTER 25

Mechanisms of action of antiepileptic drugs

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Introduction

The serendipitous discovery of the anticonvulsant properties of phenobarbital in 1912 marked the foundation of the modern pharmacotherapy of epilepsy. The subsequent 70 years saw the introduction of phenytoin, ethosuximide, carbamazepine, sodium valproate and a range of benzodiazepines. Collectively, these compounds have come to be regarded as the 'established' antiepileptic drugs (AEDs). A concerted period of development of drugs for epilepsy throughout the 1980s and 1990s has resulted (to date) in 17 new agents being licensed as add-on treatment for difficult-to-control adult and/or paediatric epilepsy, with some becoming available as monotherapy for newly diagnosed patients. Together, these have become known as the 'modern' AEDs. Throughout this period of unprecedented drug development, there have also been considerable advances in our understanding of how antiepileptic agents exert their effects at the cellular level.

AEDs are neither preventive nor curative and are employed solely as a means of controlling symptoms (i.e. suppression of seizures). Recurrent seizure activity is the manifestation of an intermittent and excessive hyperexcitability of the nervous system and, while the pharmacological minutiae of currently marketed AEDs remain to be completely unravelled, these agents essentially redress the balance between neuronal excitation and inhibition. Three major classes of mechanism are recognised: modulation of voltage-gated ion channels; enhancement of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and attenuation of glutamate-mediated excitatory neurotransmission. The principal pharmacological targets of currently available AEDs are highlighted in Table 1 and discussed further below.

Current antiepileptic drug targets*Voltage-gated sodium channels*

Voltage-gated sodium channels are responsible for depolarisation of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells. They are expressed throughout the neuronal membrane, on dendrites, soma, axons, and nerve terminals. Density of expression is highest in the axon initial segment (AIS) where action potentials are generated. Sodium channels belong to a super-family of voltage-gated channels that are composed of multiple protein subunits and which form ion-selective pores in the membrane. The native sodium channel comprises a single alpha-subunit protein, which contains the pore-forming region and voltage sensor, associated with one or more accessory beta-subunit proteins which can modify the function of the alpha-subunit but are not essential for basic channel activity. There are four predominant sodium channel alpha-subunit genes expressed in mammalian brain, denoted *SCN1A*, *SCN2A*, *SCN3A* and *SCN8A*, which encode the channels Na_v1.1, Na_v1.2, Na_v1.3 and Na_v1.6, respectively. These channels are expressed differentially in the nervous system. Na_v1.3 expression is mainly restricted to the early stages of development, while Na_v1.1 is the major sodium channel in inhibitory interneurons and Na_v1.2 and

Na_v1.6 are expressed in the AIS of principal excitatory neurons. Na_v1.2 appears to predominate in the immature brain, with Na_v1.6 becoming more prevalent during maturation. Na_v1.6 also carries a significant proportion of the persistent sodium current and may play an important role in burst firing and ictogenesis.

Table 1. Summary of molecular targets of current antiepileptic drugs (+ + + = principal target, + + = probable target, + = possible target).

	Voltage-gated Na ⁺ channels	HVA Ca ²⁺ channels	LVA Ca ²⁺ channels	Voltage-gated K ⁺ channels	GABA _A receptors	GABA Turnover	Glutamate receptors	Synaptic vesicle protein 2A	Carbonic anhydrase
Phenobarbital		+			+++		+		
Phenytoin	+++								
Ethosuximide			+++						
Carbamazepine	+++								
Sodium valproate	++		++			++			
Benzodiazepines					+++				
Vigabatrin						+++			
Lamotrigine	+++	++							
Gabapentin	+	++				+			
Felbamate	++	++			++		++		
Topiramate	++	++		+	++		++		+
Tiagabine						+++			
Oxcarbazepine	+++								
Levetiracetam		+			+			+++	
Pregabalin		++							
Zonisamide	+++		++						+
Stiripentol					+++				
Rufinamide	+++								
Lacosamide	+++								+
Eslicarbazepine acetate	+++								
Retigabine				+++					
Perampanel							+++		
Brivaracetam								+++	

Voltage-gated calcium channels

Voltage-gated calcium channels contribute to the overall electrical excitability of neurons, are closely involved in neuronal burst firing, and are responsible for the control of neurotransmitter release at pre-synaptic nerve terminals. Like sodium channels, voltage-gated calcium channels comprise a single alpha-subunit, of which at least seven are known to be expressed in mammalian brain. There are also accessory proteins, including beta- and α_2 -delta-subunits, that modulate the function and cell-surface expression of the alpha-subunit but which are not necessarily essential for basic channel functionality. Voltage-gated calcium channels are commonly distinguished on the basis of their biophysical properties and patterns of cellular expression. High-voltage-activated (HVA) channels respond to strong depolarisations and are involved in both pre-synaptic neurotransmitter release (N-, P/Q-, and R-type) and the processing of synaptic inputs at the somatodendritic level (L-type). In contrast, the low-voltage-activated (LVA) channel opens in response to modest depolarisations at or below resting membrane potential and gives rise to transient (T-type) currents which participate in intrinsic oscillatory activity. The T-type channel is highly expressed on the soma and dendrites of thalamic relay and reticular neurons where it has been postulated to underpin the rhythmic 3 Hz spike-wave discharges that are characteristic of absence seizures.

Voltage-gated potassium channels

Voltage-gated potassium channels are primarily responsible for repolarisation of the cell membrane in the aftermath of action potential firing and also regulate the balance between input and output in individual neurons. As a group, they are highly heterogeneous. More than 40 voltage-gated potassium channel alpha-subunits have been identified thus far, each of which is structurally similar to the alpha-subunits of voltage-gated sodium and calcium channels. These are classified into 12 sub-families (K_v1 to K_v12), with individual channels comprising four alpha-subunits from the same sub-family arranged around a central K^+ sensitive pore, typically in a 'two plus two' conformation. Two functional classes of voltage-gated potassium channel are well described in the literature. K_v1 to K_v4 channels are expressed in dendrites, axons and nerve terminals and carry the delayed rectifier current (I_K) that repolarises the neuronal membrane after action potential firing. In contrast, K_v7 channels are expressed in the cell soma and AIS and are responsible for the M-current, which determines the threshold and rate of neuronal firing and modulates the somatic response to dendritic inputs. Mutations in the *KCNA1* gene, which encodes the $K_v1.1$ subunit, have been implicated in episodic ataxia type 1, while mutations in *KCNQ* genes, which encode K_v7 channels, are responsible for benign familial neonatal convulsions.

Inhibitory neurotransmission

GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system and is released at up to 40% of all synapses in the brain. GABA is synthesised from glutamate by the action of the enzyme glutamic acid decarboxylase. Following release from GABAergic nerve terminals, it acts on both GABA_A and GABA_B receptors, with a net hyperpolarising or inhibitory effect. The GABA_A receptor is a ligand-gated ion channel, comprising five independent protein subunits arranged around a central anion pore permeable to chloride and bicarbonate. Nineteen GABA_A receptor subunits have been identified to date (alpha1-6, beta1-3, gamma1-3, delta, epsilon, theta, pi, and rho1-3) which come together as heteromeric pentamers to form functional channels. GABA_A receptors mediating transient, rapidly desensitising currents at the synapse (phasic receptors) typically comprise two alpha-, two beta-, and one gamma-subunit, whereas those at extra-synaptic sites and mediating long-lasting, slowly desensitising currents (tonic receptors) preferentially contain alpha4- and alpha6-subunits and a delta-subunit in place of the gamma-subunit. In contrast, the GABA_B receptor is coupled, via a G-protein, to potassium channels which mediate slow hyperpolarisation of the post-synaptic membrane. This receptor is also found pre-synaptically where it acts as an auto-receptor, with activation limiting further GABA release. GABA is removed from the synaptic cleft into localised nerve terminals and glial cells by a family

of transport proteins, denoted GAT-1, GAT-2, GAT-3, and BGT-1. Thereafter, GABA is either recycled to the readily releasable neurotransmitter pool or inactivated by the mitochondrial enzyme GABA-transaminase.

Excitatory neurotransmission

Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Following release from glutamatergic nerve terminals, it exerts its effects on three specific subtypes of ionotropic receptor in the postsynaptic membrane, designated according to their agonist specificities; AMPA, kainate and NMDA. These receptors respond to glutamate binding by increasing cation conductance resulting in neuronal depolarisation or excitation. Most AMPA and kainate receptors are permeable only to sodium ions (although some also conduct calcium, depending on their specific subunit composition) and are involved in fast excitatory synaptic transmission. In contrast, the NMDA receptor is freely permeable to both sodium and calcium ions and, owing to a voltage-dependent blockade by magnesium ions at resting membrane potential, is only activated during periods of prolonged depolarisation, as might be expected during epileptiform discharges. Metabotropic glutamate receptors perform a similar function to GABA_B receptors; they are G-protein coupled and act predominantly as auto-receptors on glutamatergic terminals, limiting glutamate release. Glutamate is removed from the synapse into nerve terminals and glial cells by a family of specific sodium-dependent transport proteins (EAAT1-EAAT5) and is inactivated by the enzymes glutamine synthetase (glial cells only) and glutamate dehydrogenase.

Other putative targets

Countless proteins and processes are involved in the regulation of the neuronal micro-environment and in maintaining the delicate balance between excitation and inhibition in the nervous system and, theoretically at least, represent additional or secondary targets for AED action. These include the enzyme carbonic anhydrase and components of the synaptic vesicle release machinery, both of which are discussed in more detail below.

Mechanisms of action of existing agents

Sodium channels.

Blockade of voltage-gated sodium channels is the most common mechanism of action among currently available AEDs. The established agents phenytoin and carbamazepine are archetypal sodium channel blockers, a mechanism they share with the newer drugs lamotrigine, felbamate, topiramate, oxcarbazepine, zonisamide, rufinamide, lacosamide, and eslicarbazepine acetate. There is also anecdotal evidence to suggest that sodium valproate and gabapentin have inhibitory effects on sodium channels. Voltage-gated sodium channels exist in one of three basic conformational states: resting, open, and inactivated. During a single round of depolarisation, channels cycle through these states in turn (resting to open, open to inactivated, inactivated to resting) and individual neurons are unable to respond to further depolarisations until sufficient numbers of their sodium channels have returned from the inactivated state to the resting state. Antiepileptic agents with sodium channel blocking properties have highest affinity for the channel protein in the inactivated state and binding slows the conformational recycling process. As a result, these drugs produce a characteristic voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing, with little effect on the generation of single action potentials. Further complexity is added by the existence of multiple inactivation pathways. Although most sodium channel blocking AEDs target fast inactivation, lacosamide and eslicarbazepine appear to prolong slow inactivation. The clinical implications of this distinction remain unclear. It has been proposed, somewhat simplistically, that the fast inactivation pathway is more prominent during physiological neuronal activity, whereas slow inactivation plays a greater role during pathological activity (i.e. during epileptiform discharges).

Calcium channels.

Voltage-gated calcium channels represent another important target for several antiepileptic agents. The efficacy of ethosuximide and zonisamide in absence epilepsy is believed to be mediated by blockade of the LVA T-type calcium channel in the soma and dendrites of thalamic relay and reticular neurons. There is anecdotal evidence that sodium valproate may have a similar action. Lamotrigine limits neurotransmitter release by blocking both N- and P/Q-types of the HVA calcium channel and levetiracetam exerts a partial blockade of N-type calcium currents, suggesting a selective effect on an as yet unidentified sub-class of this particular channel type. Phenobarbital, felbamate, and topiramate are also believed to influence HVA calcium channel conductance, though their effects are less well characterised in terms of channel subtypes or interaction with specific protein subunits. Finally, gabapentin and pregabalin also exert their effects via HVA calcium channels, but rather than interacting with a traditional channel sub-type such as N- or L-type, they appear to bind to an accessory subunit termed α_2 -delta-1, which can modulate the function of various native channels. This subunit is upregulated in dorsal root ganglion cells of the spinal cord in response to nerve injury, with selective calcium channel blockade via the α_2 -delta-1 subunit explaining the efficacy of gabapentin and pregabalin in the treatment of neuropathic pain.

Kv7 channels.

Retigabine was licensed for the add-on treatment of refractory focal epilepsy in the UK in 2011 but has subsequently been withdrawn due to the emergence of idiosyncratic adverse effects. It exerts its antiepileptic effects by activation of the K_v7 class of voltage-gated potassium channels, is specific for channels containing $K_v7.2$ to $K_v7.5$ subunits, and has particular affinity for channel assemblies containing dimers of $K_v7.2/7.3$ and $K_v7.3/7.5$ subunits. These channels underlie the M-current in seizure-prone regions of the brain, such as cerebral cortex and hippocampus. Retigabine enhances the M-current, increasing the rate at which it is activated by depolarisation and decreasing the rate at which it is subsequently de-activated. It also enhances the M-current at resting membrane potential, hyperpolarising the cell membrane and reducing overall excitability of neurons. This effect of retigabine is mediated by binding of the drug within the pore of the channel. A single amino acid (Trp236) located in the activation gate of the K_v7 alpha-subunit protein is essential and all four subunits in the channel assembly must contain a tryptophan residue at position 236 for retigabine sensitivity.

GABAA receptors.

Activation of the ionotropic GABA_A receptor resulting in an enhanced response to synaptically released GABA is a major AED mechanism. Barbiturates (e.g. phenobarbital, primidone) and benzodiazepines (e.g. diazepam, clobazam, clonazepam) share this effect, but they bind to distinct sites on the receptor complex and differentially influence the opening of the chloride ion pore. All GABA_A receptors containing at least one alpha- and one beta-subunit appear susceptible to activation by barbiturates, with only minor differences in relative sensitivity. In contrast, benzodiazepines display a much more distinct pattern of selectivity. Benzodiazepine-sensitive GABA_A receptors are typically composed of two alpha-subunits (alpha1, alpha2, alpha3 or alpha5), two beta-subunits (beta2 or beta3), and a gamma2 subunit, whereas the delta-containing GABA_A receptor which mediates tonic inhibition is entirely insensitive to benzodiazepines, as are those containing alpha4- and alpha6-subunits. Functionally, barbiturates increase the duration of chloride channel opening, while benzodiazepines increase the frequency of opening. Barbiturates are also capable of direct activation of the GABA_A receptor in the absence of GABA, an effect which is believed to underlie their sedative properties. Several other antiepileptic agents can modulate GABA responses at the GABA_A receptor. These include felbamate and topiramate (whose binding sites and subunit specificities remain unclear), stiripentol, which has recently been reported to have greatest selectivity for alpha3-beta3-gamma2 containing receptors, and levetiracetam, which indirectly influences receptor function by blocking its negative allosteric modulation by beta-carbolines and zinc.

GABA turnover.

Vigabatrin and tiagabine are modern antiepileptic agents that exert their actions by selective neurochemical effects at the inhibitory synapse, resulting in altered GABA turnover. Vigabatrin is an irreversible inhibitor of the mitochondrial enzyme GABA-transaminase which is responsible for the catabolism of GABA, whereas tiagabine prevents the removal of GABA from the synaptic cleft by blockade of GABA transport. These distinct mechanisms result in the global elevation of brain GABA concentrations and the temporarily prolonged presence of neuronally released GABA in the synapse, respectively. Although these drugs target both neurons and glial cells, vigabatrin has marginally higher affinity for neuronal GABA-transaminase, whereas tiagabine is slightly more effective in reducing glial GABA uptake. Furthermore, tiagabine is selective for the GAT-1 GABA transporter and its pharmacological effects mirror the regional distribution of this protein, with a more pronounced action in hippocampus and neocortex. Other antiepileptic agents, including sodium valproate, gabapentin and topiramate have also been reported to influence GABA turnover by increasing neurotransmitter synthesis and/or release.

Glutamate receptors.

Perampanel is the only current AED with selective effects at glutamate receptors. It is a non-competitive AMPA receptor antagonist, which binds to a site on the extracellular domain of the channel protein distinct from the glutamate recognition site. Binding of perampanel induces a conformational change in AMPA receptor subunits that limits their ability to translate agonist (i.e. glutamate) binding into channel opening. The effect is to reduce fast excitatory neurotransmission and thereby limit the ability of seizure discharges to spread. Several other antiepileptic agents exert their effects, in part, by an action on glutamatergic neurotransmission. Blockade of the NMDA subtype of glutamate receptor is believed to contribute to the pharmacological profile of felbamate, topiramate has an inhibitory action on kainate receptors, and phenobarbital has been reported to block AMPA receptors, albeit at concentrations towards the upper end of its clinical range. Although the literature contains reports that several AEDs, most notably lamotrigine, can selectively reduce glutamate release, this phenomenon is more likely related to an inhibitory action on pre-synaptic sodium and calcium channels than any specific effect on the glutamate system.

Synaptic vesicle protein 2A.

Levetiracetam was developed and licensed for the treatment of epilepsy with no clear indication of how it worked at the cellular level. A specific binding site for the drug in mammalian brain was later identified and classified as synaptic vesicle protein 2A (SV2A). This protein is now considered to be the primary target of both levetiracetam and brivaracetam, a more potent and selective analogue of levetiracetam and, at the time of writing, the most recent drug to be added to the antiepileptic armamentarium. Despite intense investigation, the precise physiological role of SV2A is still unclear and important details concerning the interaction between these drugs and the SV2A protein remain to be characterised. SV2A is known to be highly expressed in pre-synaptic nerve terminals where it is believed to contribute to the complex protein interactions involved in synaptic vesicle release and recycling. Selective binding of levetiracetam and brivaracetam to SV2A has been definitively demonstrated, with little or no affinity for other members of the same protein family, and there is also an impressive correlation between SV2A binding affinity and the anticonvulsant efficacy of a series of levetiracetam analogues in audiogenic seizure sensitive mice. Nevertheless, there is still no convincing evidence to suggest whether the interaction of these drugs with the SV2A protein is facilitatory or inhibitory or if it results in altered packaging, trafficking, membrane fusion or recycling of synaptic vesicles within the nerve terminal.

Carbonic anhydrase.

The acid-base balance and maintenance of local pH is critical to normal functioning of the nervous system. Various isoenzymes of carbonic anhydrase play an important role in this regard. They are responsible for catalysing the bi-directional conversion of carbon dioxide and water to bicarbonate

and hydrogen ions ($\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+$). The forward reaction is rapid, whereas the rate of the reverse reaction is more modest. As a result, inhibition of carbonic anhydrase influences the latter more significantly, producing a localised acidosis and increased bicarbonate ion concentration. This, in turn, attenuates excitatory neurotransmission by reducing NMDA receptor activity and enhances inhibitory neurotransmission by facilitating the responsiveness of GABA_A receptors. Acetazolamide is a classical carbonic anhydrase inhibitor which has been employed as an antiepileptic agent with some success. Topiramate and zonisamide are known to share this mechanism but are significantly less potent and have greater selectivity for individual isoenzymes (topiramate inhibits CA-II and CA-IV). Recent evidence suggests that lacosamide may also inhibit carbonic anhydrase, but this finding requires independent verification. Thus, inhibition of carbonic anhydrase can be considered as an AED mechanism of action but the extent to which it contributes to the clinical activity of individual compounds remains to be determined.

Implications of mechanisms of action

Efficacy

One of the more surprising aspects of AED pharmacology is the apparent lack of a direct relationship between mode of action and efficacy. It is, however, possible to make the following broad generalisations regarding spectrum of activity. Selective sodium channel blockers (i.e. carbamazepine, phenytoin, oxcarbazepine, lacosamide, eslicarbazepine acetate) and selective HVA calcium channel blockers (i.e. gabapentin, pregabalin) tend to have efficacy against focal seizures and primary generalised tonic-clonic seizures and are typically inactive against or can exacerbate other generalised seizure types (i.e. absence, myoclonic). This characteristic is shared with selective GABA turnover drugs (i.e. vigabatrin, tiagabine) but not with selective GABA_A receptor drugs (i.e. phenobarbital, benzodiazepines) which are additionally effective in many types of generalised epilepsy. Any compound that exerts its effects by blockade of T-type LVA calcium channels, either wholly (i.e. ethosuximide) or in part (i.e. zonisamide), is potentially effective against absence seizures and drugs with multiple mechanisms of action (i.e. sodium valproate, topiramate, zonisamide) tend to be broad spectrum with efficacy against a wide range of seizure types and in multiple syndromes. The spectrum of efficacy associated with newer AED mechanisms, such as SV2A modulation and AMPA receptor blockade, remains to be fully explored; most are licensed currently for focal and secondary generalised tonic-clonic seizures only, although levetiracetam is also approved for myoclonus.

Tolerability

All AEDs elicit dose-related adverse effects, the majority of which are CNS in origin (i.e. somnolence, dizziness, ataxia, headache). For the most part, these side effects reflect a general dampening of neuronal activity and are unconnected to specific mechanisms of action. Dizziness and diplopia are marginally more common with sodium channel blockade than with other AED mechanisms, perhaps reflecting the higher underlying frequencies of neuronal firing in cerebellum and retina, respectively. There is also anecdotal evidence to suggest that targeting slow rather than fast inactivation of the voltage-gated sodium channel is associated with fewer adverse effects, but this remains to be proven. Paraesthesia with topiramate and zonisamide is likely to correspond to their inhibition of carbonic anhydrase in the peripheral nervous system, as is their modest propensity to cause renal calculi following prolonged exposure. In addition to dose-related adverse effects, many antiepileptic agents are also associated with one or more specific, dose-independent adverse reactions. This category includes idiosyncratic skin rashes with phenytoin, carbamazepine, lamotrigine and oxcarbazepine, which are unrelated to their common blockade of sodium channels and instead reflect similarities in their chemical structures and their consequent propensity to elicit allergic reactions. At present, there is no obvious pharmacological explanation for weight gain with sodium valproate and pregabalin, weight loss with topiramate, or gingival hyperplasia with phenytoin. Other than paraesthesias and renal calculi with carbonic anhydrase inhibitors, the only

adverse reaction with a convincing link to mechanism is visual field constriction with vigabatrin, believed to be a function of its irreversible inhibition of GABA-transaminase.

Polypharmacology

While many AEDs can be categorised according to a single, principal mechanism of action, it is increasingly recognised that several agents have multiple primary effects at therapeutic concentrations (Table 1). Polypharmacology, or the possession of multiple mechanisms of action within a single molecule, is more common amongst modern antiepileptic agents than their traditional counterparts. One exception is sodium valproate, which is assumed to have multiple mechanisms of action on the basis that extensive laboratory investigations have failed to find a single mechanism that would explain its broad spectrum of clinical activity. In the case of modern drugs, such as topiramate and zonisamide, the evidence for multifactorial pharmacology is compelling. The use of AEDs with multiple mechanisms of action may confer certain advantages when treating patients with multiple seizure types or in whom the diagnosis is initially unclear. Such drugs cover multiple pharmacological bases, with limited potential for overload on any given system. This may reduce the likelihood of tolerance and increase the possibility of synergism between mechanisms but may also elevate the propensity for adverse effects.

Conclusions

The explosion in licensing of new drugs for epilepsy throughout the 1990s and the early part of this century has been paralleled by remarkable advances in our understanding of how antiepileptic agents exert their effects at the cellular level. Among currently available compounds the predominant mechanisms of action include blockade of voltage-gated sodium and calcium channels, allosteric activation of GABA_A receptors, augmentation of GABA turnover, blockade of glutamate receptors, and modulation of synaptic vesicles. This new-found pharmacological knowledge is tempered to some extent by the apparent absence of an association between mode of action and clinical activity, either in terms of efficacy or tolerability. It is possible to make some general observations, not least of which is the fact that drugs with a single selective mechanism tend to have a narrow spectrum of efficacy, although even here there are exceptions (c.f. benzodiazepines). Knowing how AEDs work has important implications for clinical practice, particularly when selecting an alternative drug to replace a previously ineffective agent or when adding a new drug to an existing regimen. Why pharmacology fails to predict clinical activity *per se* is unclear but likely reflects an as of yet incomplete understanding of both drug and disease mechanisms.

Further reading

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CHAPTER 26

Starting antiepileptic drug treatment

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The single most important consideration before starting antiepileptic medication is to be secure of the diagnosis of epilepsy based on the clinical history and, where needed supporting investigations. AED treatment should never be started as a trial to 'test' the diagnosis; this will only cause problems for you and the patient and is generally unhelpful in resolving diagnostic uncertainty.

Given a likely clinical diagnosis the next questions are when to start treatment, followed by what choice of AED. AEDs should be prescribed after a careful evaluation of the risks and benefits of treatment and a discussion with the individual patient about the merits and potential side effects of treatment¹. The decision to start medication is a major one – treatment will be for many years, often lifelong, and future withdrawal will bring its own issues around recurrence risk and driving, for instance. The decision to start will depend upon factors such as the risk of recurrence, seizure type, the risk around implication of further seizures, desire to regain a driving license and, for women, the risks of antiepileptic drugs (AEDs) and seizures in pregnancy. Antiepileptic medication is normally taken for years, and good adherence is essential to avoid withdrawal seizures. Before starting any medication, it is important to give information about side effects, drug interactions, teratogenicity and driving. It is helpful to have to hand one or two of the commonest possible side effects for each anti-epileptic drug and caution the patient about these for any new drug started and document clearly this clearly in notes and letters. Individuals need to appreciate that starting medication does not hasten the return of their driving license, and that the DVLA recommend not driving during withdrawal and for six months after stopping AEDs. Patients choosing not to start medication need to be warned of the risks of seizures including, if appropriate, SUDEP (sudden unexplained death in epilepsy).

When to start antiepileptic medication – the single seizure

When dealing with a single generalised tonic clinic seizure (GTCS) it is important to make sure that the patient has just had a single seizure by asking carefully about events or symptoms that the patient would not necessarily recognise as seizures or volunteer in the history, e.g. myoclonic jerks, stereotyped focal symptoms with retained awareness, symptoms like epigastric rising, déjà vu, periods with loss of awareness and seizure-markers from sleep.

In 2014 the ILAE task force presented a new category for epilepsy diagnosis. In addition to the established "At least two unprovoked seizures occurring more than 24 hours apart", "One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%)" was added. Examples are a single seizure occurring one month after a stroke or a single seizure with a structural abnormality, for instance a structural abnormality on MRI such as a focal cortical dysplasia, cavernoma or benign lesion e.g. dysembryoplastic neuroepithelial tumour (DNET). Whilst the ILAE task force publication does not concern itself with when to start AEDs, this new definition does have implications for the

treating clinician and should be discussed with the patient and documented. It is left to the treating clinician to apply the >60% risk of recurrence in these situations; something that can be difficult to estimate in clinic, and most clinicians would currently agree that starting AEDs after a single seizure is not appropriate in the majority of circumstances; but that very careful enquiry to elicit history of focal seizure or myoclonic jerks that had otherwise gone unremarked by the patient.

When to start antiepileptic medication - rare seizures

People who have long gaps between seizures may be treated differently to those with frequent seizures, depending on the type of seizure. For instance, a patient with GTCS, at say 5-year intervals, should in most circumstances be recommended AED treatment because the risk of injury or SUDEP; a patient with only rare focal seizures, with or without impaired awareness, may take a different view. A risk of a GTCS and attendant SUDEP risk should still be discussed in these cases. In the past, fear that having a seizure might make another more likely (similar to kindling in the rat) led some to recommend early treatment. But the multicentre study of early epilepsy and single seizures (MESS)⁴ showed that the likelihood of remission is the same if treatment is immediate or deferred. AEDs do not appear to alter the prognosis of the underlying condition.

When to start antiepileptic medication - recurrence risk

The decision to start medication is a balance between the risk of recurrent seizures and the requirement for regular medication with all that this entails. The risk is greatest close to the first seizure; individuals seen months after a seizure are already low risk. Factors associated with higher risks of recurrence include: an underlying structural abnormality, learning difficulties and spike-wave on EEG^{4,5}. The DVLA now recognise this evidence and allow individuals who have had a single seizure, in whom investigations are normal and the risk of recurrence is deemed to be low (< 20% per annum) to drive using a Class 1 (not HGV) license after six rather than 12 months.

Acute symptomatic and provoked seizures

Seizures associated with acute insults to the brain, e.g. infection or trauma, need to be treated but AED treatment should not be given to prevent the development of epilepsy because this is ineffective⁶ and AEDs should be discontinued within or at most 6 months after the insult. Seizures exclusively provoked by external factors, e.g. alcohol withdrawal, should be treated by avoiding the provocation.

Deciding to start

The diagnosis of epilepsy can be straightforward but can also be difficult in some cases. Unwitnessed attacks and subjective symptoms such as fear, or panic can cause difficulties. In almost all cases it is sensible to wait until the diagnosis is secure, 'on the balance of probabilities' and to hold off treatment if there is doubt. It should also be noted that some people choose not to take medication, e.g. a young woman with focal seizures and little if any loss of awareness who does not want to drive and is about to start a family. Relevant factors such as lifestyle, work, personal safety, driving and responsibilities for others should be discussed with the individual when deciding whether to start medication or not. This is not a consultation that should be hurried.

The aim of antiepileptic medication is to prevent seizures with minimal discomfort to the individual. All AEDs have the potential for side effects and some have significant interactions with other medication. Choice of AED will depend on these and the efficacy of the drug. Choice of AED is determined to an extent by the seizure type (s) and epilepsy syndrome (see Tables 1 and 2). A single AED should be started in a low dose and escalated - slowly - to a maintenance dose (see Table 3).

Rapid escalation is more likely to be associated with acute idiosyncratic, and dose related side effects such as drowsiness or rash that can dishearten or put the individual at risk of iatrogenic harm. Many individuals will respond to a low dose of an appropriate AED. Indeed, the response to the first well-tolerated AED helps to predict the outcome⁷. About 50% will enter a remission quickly. Of the remainder, 20-30% will enter remission with active management including alternative monotherapy or polytherapy, while the remainder have refractory epilepsy and continue to have seizures. It is helpful to talk to patients about these figures in general terms at the outset, particularly if they have factors that suggest poor prognosis. Over-optimism can lead to disillusionment and poor adherence.

Choice of AED

Industry sponsored phase 3 clinical trials of AEDs are designed to satisfy regulatory requirements for drug licensing. For ethical reasons (one cannot randomise a patient to no treatment), new AEDs can only be initially tested as add on therapy. This does not mean they are necessarily unsuitable for monotherapy, just untested and unlicensed for such. Experience is gained as add on therapy and further open studies applications for the monotherapy license is made. Research participants in phase 3 trials are generally individuals with highly refractory epilepsy (usually focal) and have frequent seizures; new medications are added into existing therapy and the randomised phase of the trial is usually three to four months with relatively rapid dose escalations. This is far removed from the typical clinical scenario of an individual with newly diagnosed epilepsy starting their first AED in monotherapy. The SANAD (Standard and New Antiepileptic Drug) study coordinated from Liverpool aimed to address this. This large pragmatic study comprised two arms: arm A compared carbamazepine with lamotrigine, topiramate, gabapentin and latterly oxcarbazepine⁸; arm B compared valproate with lamotrigine and topiramate⁹. Arm A contained individuals with predominantly focal epilepsy and arm B mostly generalised epilepsy (though unclassified epilepsies were also entered into arm B). The study was randomised but not blinded, which gives a lower evidence grade; but it is by far the largest and best-conducted study of treatment in newly diagnosed epilepsy available. And it confirmed what clinical experience suspected, i.e. no new AED in the study was more effective than carbamazepine for focal epilepsy but lamotrigine and oxcarbazepine were better tolerated. In arm B valproate was the most effective drug. The SANAD study did not include the newest AEDs because they were not widely available at the time. SANAD II has recently (2019) presented results showing sodium valproate to be superior to levetiracetam in the generalised epilepsies, and full publication of results is expected soon. Sodium valproate should never be prescribed first line in women of childbearing age unless exceptional circumstances and compliance with current MHRA guidance.

AED therapy should be chosen according to the type of seizure and tailored to the individual. It is important to characterise the seizure type and epilepsy syndrome and to avoid AEDs that might exacerbate seizures, e.g. carbamazepine in absence or myoclonic seizures in the Idiopathic Generalised Epilepsies.

Cost is a factor we cannot ignore and, if standard cheaper medication is acceptable, it should be prescribed. Generic prescribing can be problematic, more so for those already established on an AED, because minor changes in AED levels can result in breakthrough seizures, and changes in brand should be avoided where possible.

Carbamazepine should be prescribed in the modified-release preparation as this reduces side effects¹⁰. Individuals who cannot tolerate carbamazepine may tolerate oxcarbazepine, or possibly eslicarbazepine (this is not currently licensed for monotherapy in the UK) though the long-term side effect of hyponatraemia and the risk of rash are seen with both. Lamotrigine was originally promoted as 'the AED for women' and was said to have no interactions with hormonal contraceptives. This has

been shown not to be the case; it is now known that lamotrigine levels can fall unpredictably when oestrogen-containing contraceptives are used concomitantly¹¹. Similarly, lamotrigine levels can fall unpredictably in pregnancy¹². Lamotrigine is recognised to exacerbate myoclonic seizures in some individuals with JME. Valproate, the most effective drug in generalised epilepsy, is best avoided as first-line therapy in women of childbearing potential because of the higher risk of teratogenicity^{13,14}; it can also be associated with significant weight gain and extrapyramidal side effects. But in some individuals, valproate is the only drug that is effective. Levetiracetam is effective as add-on for generalised seizures¹⁵ and can be very effective for myoclonic seizures¹⁶ but there are no data for its use as first-line therapy in generalised epilepsy. Ethosuximide is the most effective AED for absence seizures, but if the individual also has generalised tonic-clonic seizures lamotrigine or valproate should be used - the latter being more effective¹⁷.

In patients who cannot tolerate the first prescribed AED then an alternative first-line AED for their seizure type should be introduced to replace the first. If the first AED is tolerated but fails to be effective several questions need to be answered before moving on to an alternative. These are:

1. Is the diagnosis of epilepsy correct?
2. Is the individual taking his or her medication?
3. Is the wrong AED for the seizure type being prescribed?
4. Has a progressive underlying condition, e.g. glioma, been missed?
5. Is there undeclared use of alcohol or drugs?

If these can be excluded the dose of the first AED needs to be increased to the level that individual can tolerate and, if the seizures continue, the dose is then usually reduced a little before a second AED is introduced and the dose titrated up. If the second AED is effective, then the original AED can gradually be withdrawn. It is good practice to change only one AED at a time so that, if for example seizures increase or worsen, the cause is clearer. Which AED should be added if the first fails is difficult to proscribe but it would seem reasonable to choose an AED with a different mechanism of action if the first has failed. Theories of 'rational polytherapy' are not supported by extensive evidence¹⁸, but it is recognised that the use of drugs with similar mechanisms of action, e.g. sodium channel blockers, can be associated with more side effects if used in high dose together.

Prognosis

The outcome for many patients starting AEDs is good with 70% entering a prolonged remission. Structural abnormalities, frequency of seizures and learning difficulties are associated with poorer outcomes¹⁹. Whether treatment alters the long-term outcome is uncertain, but studies from developing countries where the treatment gap is very wide (up to 85% not receiving medication)²⁰ suggest that the underlying nature of the epilepsy is more important, and AEDs prevent seizures but do not alter outcome.

Table 1. Choice of AED by seizure type.

Seizure type	First-line drugs	Adjunctive drugs	Drugs to be avoided (may worsen seizures)
Focal with/without secondary generalisation	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate Perampanel Brivaracetam	
Generalised tonic-clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Topiramate	(if there are absence or myoclonic seizures, or if JME suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	Levetiracetam Sodium valproate	Levetiracetam Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Table 2. Choice of AED for common epilepsy syndromess.

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	AEDs to avoid (may worsen seizures)
Childhood absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Juvenile absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Levetiracetam Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Epilepsy with generalised tonic-clonic seizures only	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate	
Idiopathic generalised epilepsy	Lamotrigine Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	

Table 3. Starting and maintenance doses and common side effects for first-line AEDs.

Drug	Starting dose/day	Typical maintenance dose/day	Dosing interval	Commonest side effects
Carbamazepine MR (modified release)	200 mg	400–1800 mg	b.d.	Rash Diplopia Dizziness Headache Nausea Hyponatraemia
Ethosuximide	250 mg	500-2000 mg	b.d.	Nausea Drowsiness Headache
Lamotrigine	25 mg	100-400 mg	b.d.	Rash (always caution patients and document this, as persisting with the drug in the face of rash can lead to severe Stephens Johnson Syndrome) Nausea Dizziness Headache Insomnia
Levetiracetam	250 mg	1000–3000 mg	b.d.	Lethargy Irritability Mood disturbance Insomnia Drowsiness Unsteadiness
Sodium valproate	300 mg	600-2500 mg	b.d.	Weight gain Tremor Hair loss Teratogenesis

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CHAPTER 27

Managing refractory epilepsy

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Refractory or drug resistant epilepsy develops in 20–30% of all patients diagnosed with epilepsy. A wealth of evidence and guidelines (including the NICE and SIGN guidelines in the UK) state that a person should be considered to have refractory epilepsy if they have failed to achieve sustained seizure freedom with two appropriate and tolerated antiepileptic drug (AED) regimens¹. Outcome studies have consistently shown response to the first AED to be a strong predictor of long-term outcomes. In a series of patients with newly diagnosed epilepsy in Glasgow, the response rate to the first, second and third AED was 50.4%, 10.7% and 2.7%, respectively². A small proportion of patients may respond well to further changes in treatment, but in the majority, refractory epilepsy can be identified relatively early in the course of the disorder.

Refractory epilepsy, as reflected in the title of this course, is a multifaceted disorder. Patients not only suffer the physical consequences of seizures, but psychological, cognitive and societal ones as well³. Patients with refractory epilepsy are less likely to acquire qualifications, be employed, married, or live independently⁴. Management of this complex disorder requires appreciation not only of its physical manifestations, but also the psychological, psychiatric and societal aspects of the condition. The clinician requires insights into everything from the neuropharmacology of AEDs to the working of clinical commissioning groups. This may sound challenging, but can make for a fulfilling and rewarding career.

This chapter aims to give an overview of a practical approach to managing refractory epilepsy. Details of management of the various aspects of the condition may be found in other chapters.

General principles of managing refractory epilepsy

1. Review the diagnosis and classification
2. Review AEDs currently and previously used
3. Consider non-pharmacological treatments
4. Address co-morbidities and lifestyle issues
5. Optimise quality of life.

Reviewing diagnosis - living with uncertainty

A significant proportion of patients who are said to have refractory epilepsy do not have epilepsy⁵. Therefore, when AEDs fail to achieve seizure control, it is essential that the diagnosis is reviewed. The main consideration here is non-epileptic attack disorder (NEAD). It is often difficult from descriptions alone to be certain as to whether seizures are epileptic or non-epileptic. This diagnostic uncertainty is one of the major challenges a clinician has to face in managing patients presenting with apparent drug-resistant epilepsy.

Epileptic seizures are thought to co-exist with non-epileptic seizures in 15–50% of cases^{6,7}. The mainstay of diagnosis remains a detailed history. The clinician should aim to recreate the episode in as much detail as possible, both from the patient’s perspective, and that of an eyewitness. Conversation analysis has identified differences in the way NEAD sufferers articulate the description of the seizures, compared to those with epileptic seizures⁸. With experience, one learns to identify non-verbal clues during the clinical encounter that can be diagnostically helpful.

Increasingly, video recordings, particularly on mobile phones, are available. There are caveats to their use, mainly the fact that the beginning of the attack is usually missed, but these recordings are easily available, and in most cases are superior to descriptions alone. Other sources of video recordings, including CCTV footage, can be diagnostically useful. Time and effort spent in trying to obtain such footage could be well worth it.

Formal diagnostic video telemetry (VT), capturing all the different types of attacks experienced by the patient, remains the gold standard investigation in clarifying the diagnosis. However, most epilepsy monitoring units based in acute hospitals can only admit patients for a week or two, and it is common for patients to have no, or only some attacks. Thus, information from VT usually only forms part of the diagnostic work up. Longer-term monitoring over several weeks can currently be performed only at the NSE in London, and at Scottish Epilepsy Centre in Glasgow; selected cases may require referral to these centres for diagnostic clarification.

Whichever method is used for reviewing the diagnosis, the objective is to achieve a clear understanding of the nature of each type of episode, which the patient and their family members/carers are also able to understand. This should then enable appropriate management of each type of seizure. It is especially important to have a written care plan for each type of attack where epileptic and non-epileptic attacks co-exist, and where professional carers are involved (see Figure 1 for an example). This document should be available to all involved in the patient’s care (patient/carer, GP, hospital notes) so that each type of attack can be managed appropriately, and the risk of iatrogenic harm minimised. Involvement of an epilepsy nurse specialist can be invaluable in this process.

Table 1. Care plan for management of seizures and behavioural attacks in a patient with moderate learning difficulties and refractory epilepsy due to tuberous sclerosis.

Type of event	Classification	Management
Brett’s body stiffens, lips turn blue, right arm and leg may shake. Unresponsive. Usually lasts 1–2 minutes. Can occur repeatedly. May evolve into	Generalised tonic or tonic-clonic seizure	If attack does not settle within 2–3 minutes, buccal midazolam 10 mg to be administered, as per protocol for management of prolonged seizures
Brett screams and bites his arm. May stop responding for a few minutes. Can go on for 15–30 minutes.	Non-epileptic	Anti epileptic drugs should not be administered. Behaviour management as suggested by LD team.
Brett looks pale and has reduced responsiveness. May make lip smacking movements. Lasts 5–6 minutes. Usually occurs in clusters of 5–6 per day.	Complex partial seizures	Following first episode, oral clobazam 10 mg to be administered, to prevent clusters.

Epilepsy by itself cannot be a diagnosis; it is merely a symptom of a brain disorder. Once it is confirmed that the patient’s attacks are epileptic seizures, all efforts should be made to identify the aetiology. The age of onset, types of seizures, and EEG patterns may allow identification of a genetic generalised epilepsy syndrome (e.g. juvenile myoclonic epilepsy, JME). State of the art MRI scans, reviewed by a neuroradiologist, will be able to identify epileptogenic lesions in about two-thirds of all cases⁹. In patients with adult onset epilepsy, where no epileptogenic lesions can be identified on MRI scans of adequate quality, consideration should be given to testing for autoimmune causes¹⁰. Immunotherapy may have a role in the treatment of seizures in patients who test positive for antibodies to neuronal antigens.

Review of the diagnosis is an ongoing process. The description of each type of event, and a clinical impression as to whether they are epileptic or not, as well as the frequency of each type, should be documented at each encounter. One should always be prepared to change the diagnosis in the light of any new information that emerges. It helps to have a consistent system of documentation, and to use this at each patient encounter. The ILAE’s multi-axial diagnostic scheme is ideal for this purpose (see Figure 2 for an example).

Review of AEDs, present and past

It goes without saying that, once the diagnosis has been made, one should ascertain that the AED used is appropriate for the type of epilepsy. Sodium channel blocking drugs and GABA-ergic drugs can worsen seizures in generalised epilepsies, and tiagabine has been associated with episodes of non-convulsive status epilepticus in patients with focal and generalised epilepsies¹¹. Idiosyncratic seizure exacerbations can rarely occur with all drugs.

Neurologists frequently ‘inherit’ patients with refractory epilepsy from colleagues, or have patients referred for specialist opinion. In these situations, it can be difficult to ascertain the details of previous drug therapy, which may require further correspondence with the GP. Efforts made in this regard can often identify useful therapeutic options (e.g. a patient with refractory focal epilepsy who has never taken lamotrigine). This is also important in determining AEDs that may be associated with a high risk of severe adverse effects (e.g. oxcarbazepine and eslicarbazepine are best avoided in a patient with a history of allergic rash with carbamazepine).

Seizure types and frequency:	Focal aware seizure (right arm clonic)	-1 per week
	Focal – bilateral convulsive seizure	-1 per year
Epilepsy Classification:	Left frontal epilepsy secondary to traumatic brain injury	
Antiepileptic medication:	Lamotrigine 200mg BD	
	Zonisamide 150mg BD	
Medical / psychiatric comorbidity:	Depression – on venlafaxine 75 mg	
	Chronic migraine – on Botox therapy	

Figure 2. Documentation of epilepsy diagnosis in the header of an outpatient clinic letter, using the ILAE semiologic classification.

In patients with refractory epilepsy, potential efficacy in controlling seizures is not the only consideration in choosing AEDs. In many cases, adverse effects from AEDs impair patients' quality of life more than seizures themselves¹². It is therefore important to discuss with patients the most common, as well as most serious, adverse effects reported with any AED before commencing treatment. In addition, many co-morbidities of epilepsy can be affected by AEDs (e.g. cognition, mood, bone health), which will need to be taken into account when deciding on an AED.

Many patients with refractory epilepsy will be on combinations of AEDs. There is little empirical evidence to guide the choice of combination therapy. In the absence of evidence, the notion of 'rational polytherapy' has gained currency¹³. This is based on the mechanism of action (MoA) of AEDs (or more precisely their molecular pharmacological effects – whether this is the same as the mechanism of anti-seizure activity in all cases is a moot point), and involves combining drugs that have differing MoA, while avoiding those that have the same or similar MoA. There is some evidence that this approach reduces the incidence of neurotoxic side effects¹⁴. The combination of valproate with lamotrigine can be synergistic, which can translate into greater efficacy, as well as greater potential for adverse effects. However, a number of other factors including patient preference may be more important than molecular pharmacology in determining the efficacy of combinations. Clinical pragmatism is likely to be a more successful basis for choosing AED combinations than the dogma of mechanistic rationalism.

Non pharmacological treatments

All patients with refractory epilepsy should be reviewed in a specialist service to consider suitability for non-pharmacological treatments, including epilepsy surgery. Suitability for surgery cannot be assessed without expert review of seizure semiology, epilepsy classification and imaging. The process of evaluation for epilepsy surgery is discussed in detail elsewhere in this textbook.

Neuromodulation is an option for patients with refractory epilepsy who are not candidates for resective surgery. Vagal nerve stimulation remains the most widely used modality, and can help reduce seizure frequency in a proportion of patients with refractory epilepsy. Deep brain stimulation (targeting the anterior nucleus of the thalamus) has been licensed as a therapeutic option for patients with epilepsy in the UK. Closed-loop responsive neurostimulation (RNS) systems are also on the horizon¹⁵. There is likely to be further refinement in the techniques of neurostimulation in the years ahead.

Address co-morbidities

Depression and anxiety

Depression is the most common co-morbidity of epilepsy, with a lifetime incidence of up to 35%. There is a growing body of evidence to suggest an organic link between temporal lobe seizures and depression^{16,25}. Patients with temporal lobe epilepsy are particularly at risk of dysphoric disorders, including suicidality. Data from outcome studies also show worse outcomes from medical and surgical treatment for epilepsy in patients with depression. Depression significantly impairs patients' quality of life, and is often untreated in patients with epilepsy due to the erroneous belief among non-specialists that antidepressants of the SSRI or TCA classes adversely affect seizure control^{17,18}. Neurologists should take responsibility for managing much of the psychiatric co-morbidity of epilepsy as the reality, all too frequently, is that no one else will.

Cognition

Cognitive disorders frequently coexist with epilepsy, and can impair patients' ability to function normally, even when the seizure burden is reduced. These are frequently due to the underlying cause of the epilepsy itself, and therefore should be regarded as another symptom of the underlying

brain disorder. Cognitive problems can be very obvious, as in patients with learning disability, but in many cases can be subtle. There is mounting evidence that cognitive problems occur even in the so-called idiopathic epilepsies, where brain structure and function has traditionally been thought to be normal¹⁹. Advanced neuroimaging has identified structural correlates of cognitive deficits in patients with IGE syndromes. Similarly, patients with temporal lobe epilepsy (TLE) often describe memory problems, which can take the form of accelerated long-term forgetting (ALF), transient epileptic amnesia (TEA) and remote memory impairment²⁰.

In addition to fixed deficits related to the underlying brain disorder, patients with epilepsy also experience dynamic changes, associated with seizures and inter-ictal epileptiform activity, as well as adverse effects of AED. Many patients with apparently well controlled seizures and cognitive impairment show ongoing inter-ictal discharges, abolition of which may improve cognitive profile²¹. Older AEDs, especially barbiturates, and topiramate among newer AEDs, are most likely to cause cognitive adverse effects²². Input from a neuropsychologist with expertise in epilepsy can be very helpful in characterising cognitive difficulties, and suggesting compensatory strategies for patients.

Metabolic disorders

AEDs can have a variety of metabolic effects, which need to be monitored for in patients on long-term AED therapy. These include effects on bone metabolism, reproductive function (including sexual dysfunction, contraception and pregnancy issues) and cardiovascular risk. Many of these effects are mediated through the induction of hepatic microsomal enzymes, and can be minimised by avoiding the use of such AEDs²³. Valproate, which is a hepatic enzyme inhibitor, constitutes a special case when it comes to metabolic effects²⁴. Impairment of glucose metabolism, weight gain, tremor (including Parkinsonism) and high teratogenicity are particular features of this drug.

Lifestyle issues

The impact of refractory epilepsy on the individual's life can be highly variable. Depending on their individual circumstances, the majority of patients will benefit from support with education, employment, leisure etc. The services of an epilepsy specialist nurse, ideally community based, with links to neurology services, would be invaluable in this regard.

Optimise quality of life

The overall objective of the various management strategies outlined above is to optimise patients' quality of life. Seizure freedom correlates most strongly with improvement in quality of life for people with epilepsy, but in the population of patients under discussion, this is sadly unlikely to be achieved. The physician has to identify the specific areas where help can be provided, being aware that this involves much more than prescribing drugs. Providing a sympathetic ear, practical advice and directing to external agencies such as voluntary organisations can be equally if not more appreciated by patients.

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CHAPTER 28

Overview of established antiepileptic drugs

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Established antiepileptic drugs (AEDs) are those which were licensed before 2000. By now, substantial data have accumulated on them. Their pharmacokinetic properties are listed in Table 1, and indications and a guide to dosing in children, adults and adolescents are outlined in Tables 2 and 3, respectively. These drugs are not without their hazards and their optimum use must be governed by an appreciation of their potential for dose-related and idiosyncratic toxicity (see table 4). The clinical use of each drug will be considered, highlighting the practical problems likely to be encountered during every day clinical use.

Carbamazepine

Carbamazepine is indicated for focal seizures and generalised tonic-clonic seizures. It is not effective, and may even be deleterious, for some people with absences and myoclonic seizures.

Carbamazepine, as a strong auto-inducer, should be introduced in low dosage (100–200 mg daily) to allow tolerance to develop to its CNS side effects. The dose can then be increased in 1–2 weekly increments of 100–200 mg/day to a maintenance dose that completely controls seizures.

Diplopia, headache, dizziness, nausea and vomiting are the commonest side effects of carbamazepine, some of which may be due to its active epoxide metabolite. Peak levels often result in intermittent side effects occurring around two hours after dosing, necessitating administration three or four times daily in some. These problems can often be overcome by prescribing the controlled-release formulation, which can be given twice daily.

Carbamazepine can cause a range of idiosyncratic reactions, the most common of which is a skin rash, occurring in up to 10% of people exposed to it. Slow dosage titration reduces the risk. Rarely, it may cause more severe skin eruptions including erythema multiforme and Stevens-Johnson syndrome. Reversible mild leucopenia often occurs and has no clinical significance. Discontinuation of therapy is not required unless accompanied by evidence of infection or if the cell count is well below $2 \times 10^9/L$. Blood dyscrasias and toxic hepatitis occur very rarely.

There are some long-term problems with carbamazepine. As a strong enzyme inducer it has the potential to affect bone health in the long term and this needs to be taken into account particularly if lifelong treatment is a consideration. At high levels, carbamazepine has an antidiuretic hormone-like action that can result in fluid retention in people with cardiac failure and in the elderly. Mild hyponatraemia is usually asymptomatic, but if serum sodium falls below 125 mmol/L there might be confusion, peripheral oedema and worsening seizure control. Cardiac arrhythmia is also an occasional complication.

Table 1. Pharmacokinetics of established antiepileptic drugs.

DRUG	ABSORPTION (BIOAVAILABILITY)	PROTEIN BINDING (% bound)	ELIMINATION HALF-LIFE (hours)	ROUTE(S) OF ELIMINATION	COMMENTS
CARBAMAZEPINE	Slow absorption (75-85%)	70-80	24-45 (single) 8-24 (chronic)	Hepatic metabolism Active metabolite	Enzyme inducer Metabolic autoinduction
CLOBAZAM	Rapid absorption (90-100%)	87-90	10-30	Hepatic metabolism Active metabolite	Sedative Tolerance
CLONAZEPAM	Rapid absorption (80-90%)	80-90	30-40	Hepatic metabolism	Sedative Tolerance
ETHOSUXIMIDE	Rapid absorption (90-95%)	0	20-60	Hepatic metabolism 25% excreted unchanged	More rapid clearance in children
GABAPENTIN	Rapid initial absorption	0	5-7	Not metabolised Excreted unchanged	Limited absorption at high doses
LAMOTRIGINE	Rapid absorption (95-100%)	50-55	14-88	Hepatic metabolism by glucuronidation	Half-life dependent on co-medication
PHENOBARBITAL	Slow absorption (95-100%)	48-54	72-144	Hepatic metabolism 25% excreted unchanged	Enzyme inducer Sedative Tolerance
PHENYTOIN	Slow absorption (85-90%)	90-93	9-40	Saturable hepatic Metabolism	Enzyme inducer Elimination half-life concentration-dependent
SODIUM VALPROATE	Rapid absorption	88-92	7-17	Hepatic metabolism Active metabolites	Enzyme inhibitor Concentration-dependent protein binding
TIAGABINE	Rapid absorption	87-96	4-9	Hepatic metabolism	
TOPIRAMATE	Rapid absorption	15	12-30	Mostly hepatic metabolism, with renal excretion. No active metabolites	Cognitive slowing, kidney stones, weight loss. Clearance increased by enzyme inducers
VIGABATRIN	Rapid absorption (60-80%)	0	5-8	Not metabolised 85% excreted unchanged	Visual field constrictions

Table 2. Dosage guidelines for established antiepileptic drugs in children.

DRUG	INDICATIONS	STARTING DOSE (mg/kg/day)	STANDARD MAINTENANCE DOSE (mg/kg/day)	DOSAGE INTERVAL
CARBAMAZEPINE	Partial and generalised tonic-clonic seizures	5	10-25	bid-qid
CLOBAZAM	Partial and generalised seizures	0.25	0.5-1	od-bid
CLONAZEPAM	Myoclonic epilepsy Lennox-Gastaut syndrome Infantile spasms Status epilepticus	0.025	0.025-0.1	bid-tid
ETHOSUXIMIDE	Generalised absences	10	15-30	od-bid
GABAPENTIN	Partial seizures	10	25-35	tid
LAMOTRIGINE	Partial and generalised seizures	with valproate 0.2 without valproate 2.0	1-5 5-15	od-bid
PHENOBARBITAL	Partial and generalised seizures Newborn seizures Status epilepticus	4	4-8	od-bid
PHENYTOIN	Partial and generalised tonic-clonic seizures Status epilepticus	5	5-15	od-bid
PRIMIDONE	Partial and generalised tonic-clonic seizures	10	20-30	od-bid
SODIUM VALPROATE	Partial and generalised seizures	10	15-40	od-tid
TOPIRAMATE	Partial and generalised seizures	2	3-6	od-bid
VIGABATRIN	Partial seizures Infantile spasms	40	50-100	bid

Table 3. Dosage guidelines for established antiepileptic drugs in adolescents and adults.

DRUG	INDICATIONS	STARTING DOSE	STANDARD MAINTENANCE DOSE	DOSAGE INTERVAL	TARGET RANGE
CARBAMAZEPINE	Partial and generalised tonic-clonic seizures	200 mg	400-2000 mg	*od-qid	25-50 mmol/L (6-12 mg/L)
CLOBAZAM	Partial and generalised seizures	10 mg	10-40 mg	od-bid	None
CLONAZEPAM	Myoclonic and generalised tonic-clonic seizures	1 mg	2-8 mg	od-bid	None
ETHOSUXIMIDE	Absence seizures	500 mg	500-2000 mg	od-bid	283-708 mmol/L (40-100 mg/L)
GABAPENTIN	Partial seizures	300-400mg	1800-3600 mg	tid	None
LAMOTRIGINE	Partial seizures and generalised tonic-clonic seizures	25mg	200-400mg	bid	6-16 mg/L
PHENOBARBITAL	Partial and generalised tonic-clonic, myoclonic, clonic and tonic seizures Status epilepticus	60 mg	60-240 mg	od-bid	40-172 mmol/L (10-40 mg/L)
PHENYTOIN	Partial and generalised tonic-clonic seizures Status epilepticus	200 mg	100-700 mg	od-bid	40-80 mmol/L (10-20 mg/L)
PRIMIDONE	Partial and generalised tonic-clonic seizures	250 mg	250-1500 mg	od-bid	23-55 mmol/L (5-12 mg/L)
SODIUM VALPROATE	All generalised seizures Partial seizures	500 mg	500-3000 mg	*od-bid	347-693 mmol/L (50-100 mg/L)
TIAGABINE	Partial seizures	5-10 mg	30-45 mg	tid	
TOPIRAMATE	Partial and generalised seizures	25 mg	100-400 mg	bid	6-74 mmol/L (2-25 mg/L)
VIGABATRIN	Partial seizures	500 mg	1000-4000 mg	od-bid	None

*od or bid with controlled-release formulation

Table 4. Side effects of established antiepileptic drugs.

CARBAMAZEPINE	CLOBAZAM	CLONAZEPAM	ETHOSUXIMIDE	GABAPENTIN	LAMOTRIGINE	PHENOBARBITAL
<ul style="list-style-type: none"> * Diplopia * Dizziness * Headache * Nausea Drowsiness Neutropenia Hyponatraemia Hypocalcaemia Orofacial dyskinesia Cardiac arrhythmia 	<ul style="list-style-type: none"> * Fatigue * Drowsiness Dizziness Ataxia Irritability Aggression Hypersalivation Bronchorrhoea Weight gain Muscle weakness Psychosis 	<ul style="list-style-type: none"> * Fatigue * Sedation * Drowsiness Dizziness Ataxia Irritability Aggression (children) Hyperkinesia (children) Hypersalivation Bronchorrhoea Psychosis 	<ul style="list-style-type: none"> * Nausea Anorexia Vomiting Agitation Drowsiness Headachew Lethargy 	<ul style="list-style-type: none"> * Somnolence * Dizziness * Ataxia * Fatigue Diplopia Paraesthesia Amnesia 	<ul style="list-style-type: none"> * Drowsiness * Diplopia * Headache * Ataxia * Insomnia * Tremor Nausea Vomiting Aggression Irritability 	<ul style="list-style-type: none"> * Fatigue * Listlessness * Tiredness * Depression * Insomnia (children) * Distractibility (children) * Hyperkinesia (children) * Irritability (children) Aggression Poor memory Decreased libido Impotence + Folate deficiency Neonatal haemorrhage Hypocalcaemia Osteomalacia
<ul style="list-style-type: none"> * Morbilliform rash Agranulocytosis Aplastic anaemia Hepatotoxicity Photosensitivity Stevens-Johnson syndrome Lupus-like syndrome Thrombocytopenia Pseudolymphoma Teratogenicity 	<ul style="list-style-type: none"> Rash 	<ul style="list-style-type: none"> Rash Thrombocytopenia 	<ul style="list-style-type: none"> Rash Erythema multiforme Stevens-Johnson syndrome Lupus-like syndrome Agranulocytosis Aplastic anaemia 	<ul style="list-style-type: none"> * Increased seizures 	<ul style="list-style-type: none"> * Rash Stevens-Johnson Syndrome Toxic epidermal necrolysis Liver failure Aplastic anaemia Pancytopenia Multi-organ failure 	<ul style="list-style-type: none"> * Macropapular rash Exfoliation Toxic epidermal necrolysis Hepatotoxicity Frozen shoulder Teratogenicity

Above line: Dose-related; Below line: Idiosyncratic; *Commonest side effects

Continued

Table 4 (continued). Side effects of established antiepileptic drugs.

PHENYTOIN	PIRACETAM	PRIMIDONE	SODIUM VALPROATE	TIAGABINE	TOPIRAMATE	VIGABATRIN
* Nystagmus * Ataxia Anorexia Dyspepsia Nausea Vomiting Aggression Depression Drowsiness Headache Paradoxical seizures Megaloblastic anaemia Hyperglycaemia Hypocalcaemia Osteomalacia + Neonatal haemorrhage	* Diarrhoea * Weight gain Insomnia Depression Hyperkinesia	* Fatigue * Listlessness * Tiredness * Depression * Psychosis * Decreased libido * Impotence * Hyperkinesia (children) * Irritability (children) Nausea Vomiting Nystagmus Ataxia Folate deficiency Hypocalcaemia Osteomalacia + Megaloblastic anaemia Neonatal haemorrhage	* Tremor * Weight gain * Hair loss Anorexia Dyspepsia Nausea Vomiting Alopecia Peripheral oedema Drowsiness Hyperammonaemia Amenorrhoea	* Dizziness * Headache * Tremor * Difficulty concentrating Light-headedness * Nervousness Asthenia Abnormal thinking	* Anorexia * Weight loss * Impaired concentration Impaired speech Paraesthesias Kidney stones Impaired memory Ataxia	* Drowsiness * Fatigue * Headache * Ataxia * Nystagmus * Diplopia * Irritability * Depression Psychosis Aggression Weight gain Stupor Tremor Impaired concentration
* Rash * Acne * Gum hypertrophy * Coarse facies * Hirsutism Blood dyscrasias Lupus-like syndrome Reduced serum IgA Pseudolymphoma Peripheral neuropathy Stevens-Johnson syndrome Dupuytren's contracture Hepatotoxicity Teratogenicity		Rash Agranulocytosis Thrombocytopenia Lupus-like syndrome Teratogenicity	Acute pancreatitis Hepatotoxicity Thrombocytopenia Stupor Encephalopathy Teratogenicity Polycystic ovarian syndrome	Increased seizures Non-convulsive status		* Visual field defects Increased seizures

Above line: Dose-related; Below line: Idiosyncratic; *Commonest side effects; +Maternal treatment

As well as inducing its own metabolism, carbamazepine can accelerate clearance of a number of other lipid-soluble drugs including the oral contraceptive pill, necessitating, for most women, a daily oestrogen dose of 50 µg or more. Other affected drugs include sodium valproate, ethosuximide, corticosteroids, anticoagulants, antipsychotics and cyclosporin. Drugs that inhibit carbamazepine metabolism and which may result in toxicity include phenytoin, cimetidine, danazol, dextropropoxyphene, diltiazem, erythromycin, isoniazid, verapamil and viloxazine. The less common neurotoxic interaction with lithium (confusion, disorientation, drowsiness, ataxia, tremor, hyperreflexia) is not associated with altered concentrations of either drug.

The substantial variation in carbamazepine concentrations in any given individual over the course of the day - as much as 100% with twice-daily dosing using the regular release formulations - makes the interpretation of levels problematical. In most people, the dosage can be titrated adequately on clinical criteria alone. Exceptions include people with learning disabilities, those in whom adherence to treatment is suspect, and those taking a cocktail of AEDs likely to interact with each other.

Clobazam

Clobazam is a useful adjunctive drug in refractory epilepsy although the majority of responders will develop tolerance to its antiepileptic action. Nevertheless, a useful proportion (up to 20–30%) will become and stay seizure-free in the long term. There is some evidence that the intermittent use of clobazam reduces the likelihood of tolerance. Short-term administration, e.g. 10–20 mg daily for 3–7 days, can be useful in women with catamenial seizures and as ‘cover’ for special events such as holidays, weddings and surgery. A single dose of 20–30 mg can have a prophylactic action if taken immediately after the first seizure in people who suffer regular clusters of complex partial or secondary generalised seizures.

Clobazam’s structure differs from that of other benzodiazepines, and this may account for its lesser propensity to cause sedation. Nevertheless, tiredness, irritability and depression are commonly reported. Occasionally deterioration in behaviour and mood disturbance can occur, particularly in people with learning disabilities in whom clobazam should probably be avoided. Withdrawal seizures can also be a problem.

Clonazepam

Clonazepam has efficacy against absences, myoclonic jerks and tonic-clonic seizures. Sedation and tolerance, however, substantially reduce its usefulness. Few people respond well to this drug but nearly 50% will have an exacerbation of seizures when it is withdrawn. Accordingly, clonazepam now has a limited role in the management of epilepsy, possibly limited to refractory myoclonic seizures. Like other benzodiazepines, clonazepam should only be prescribed as a last resort in people with learning difficulties.

Ethosuximide

Ethosuximide is only indicated in the treatment of absence seizures. Slow introduction is sensible to minimise the development of gastrointestinal and CNS side effects. In children over six years, 500 mg daily is a reasonable starting dose, with further increments as necessary to a maximum of 1–2 g per day. The dose can be increased every 2–4 weeks according to clinical need.

Side effects usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain) or CNS (lethargy, dizziness, and ataxia). Blood dyscrasias have been reported rarely. Drug monitoring is not indicated unless for checking of adherence to treatment. Ethosuximide itself does not

interfere with drug metabolism, but provides a target for enzyme inducers such as phenytoin and carbamazepine, or inhibitors such as sodium valproate.

Gabapentin

Gabapentin may occasionally be useful as a second-line treatment of focal seizures. It is of no use in other seizure types. The initial dose is 300–400 mg/day and the titration rate consists of weekly dose increases of 300–400 mg up to 2400–3600mg/day in first instance. In view of its short elimination half-life a three times daily dosage is recommended.

Gabapentin is not metabolised, exhibits no protein binding and does not induce hepatic enzymes. Its potential for drug interaction is small and, to date, no clinically significant interaction with other drugs has been reported. Gabapentin may, therefore, be a useful add-on drug in people with a high risk of drug interactions. There is no need to measure levels as a guide to dosing.

Side effects of gabapentin are mainly related to the CNS and these include drowsiness, dizziness, diplopia, ataxia and headaches. Gabapentin is associated with weight gain, particularly at high doses. It may also occasionally worsen seizures, particularly myoclonic seizures. Gabapentin treatment has not been associated with any serious idiosyncratic reaction to date.

Lamotrigine

Lamotrigine is a first-line drug for people with focal seizures and with generalised seizures.

The recommended starting dose as monotherapy is 25 mg/day. If the person is taking concomitant sodium valproate then the starting dose should be 25 mg/day on alternate days. The maximum recommended dose as monotherapy is 400–500 mg/day in two divided doses but no more than 200 mg/day if the person is taking concomitant valproate. Treatment should be slowly titrated upwards over a period of several weeks as too rapid titration may be associated with an increased incidence of adverse events, particularly skin rash.

Lamotrigine does not seem to interact with other concomitantly administered AEDs, although it may increase levels of an active metabolite of carbamazepine. Hepatic enzyme inducers, however, increase lamotrigine clearance, reducing its half-life. Hence, higher doses of lamotrigine need to be used with concomitant enzyme inducing drugs such as phenytoin and carbamazepine. Inhibitors of hepatic enzymes, such as sodium valproate, block the metabolism of lamotrigine so that reduced doses of lamotrigine have to be used if both drugs are given together. Oral contraceptives containing oestrogen may increase the metabolism of lamotrigine.

Headaches, drowsiness, ataxia, diplopia, insomnia, nausea and dizziness are the most common acute adverse effects of lamotrigine, particularly during dose escalation. A skin rash is the commonest idiosyncratic side effect and affects up to 5% of people exposed to it. The incidence is higher when lamotrigine is used in combination with sodium valproate or if larger initial doses of lamotrigine are used. Rarely, it may cause more severe idiosyncratic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, aplastic anaemia and liver failure.

Phenytoin

Phenytoin is now a last resort option for focal and tonic-clonic seizures in view of its chronic toxicity and kinetic profile. Phenytoin is one of a handful of drugs that switches from first-order to saturation kinetics at therapeutic dosage. Accordingly, at higher levels a moderate increment in dose can produce an unexpectedly large rise in the level with accompanying neurotoxicity.

Conversely, levels can fall precipitously when the dose is reduced modestly, resulting sometimes in unexpected deterioration in seizure control. The dosage producing the same levels, therefore, varies substantially among different individuals.

Phenytoin can produce a range of dose-related and idiosyncratic adverse effects including rash, hepatotoxicity and blood dyscrasias. Reversible cosmetic changes (gum hyperplasia, acne, hirsutism, facial coarsening), although often mild, can be troublesome. Phenytoin is an enzyme inducer and as such may impact on bone health. Symptoms of neurotoxicity (drowsiness, dysarthria, tremor, ataxia, cognitive difficulties) become increasingly likely with higher levels but the diagnosis of phenytoin toxicity should be made on clinical grounds and not assumed from a high level. The person may complain of mental slowing and unsteadiness, and neurological examination may show cerebellar signs. Permanent cerebellar damage may be a consequence of chronic toxicity, so it is important to examine regularly the person taking it. In some of these people, cerebellar atrophy will be apparent on brain imaging, although hard evidence for cause and effect is not readily available. A paradoxical increase in seizure frequency may also occur with marked phenytoin toxicity.

It can accelerate the metabolism of a number of lipid-soluble drugs, including carbamazepine, sodium valproate, ethosuximide, anticoagulants, steroids and cyclosporin. Due to its saturable metabolism, phenytoin provides a target for drugs such as allopurinol, amiodarone, cimetidine, imipramine and some sulphonamides. Protein binding displacement interactions with AEDs are only clinically relevant when there is concomitant enzyme inhibition, as is the case with the combination of phenytoin and sodium valproate.

Phenobarbital

Phenobarbital is an established treatment for focal and tonic-clonic seizures but is seldom currently used in developed countries due to its potential to cause neurotoxicity.

Phenobarbital is an easy drug to use clinically. To minimise sedation, a low dose should be started (30 mg in adolescents and adults), which can be increased gradually (15–30 mg incremental steps) according to clinical requirements. The value of measuring its levels is limited, as concentration associated with seizure control varies considerably. In addition, the development of tolerance to its CNS side effects makes the toxic threshold imprecise.

The major problem in the clinical use of phenobarbital is its effect on cognition, mood and behaviour. It can produce fatigue, listlessness and tiredness in adults and insomnia, hyperactivity and aggression in children (and sometimes in the elderly). Subtle impairment of memory, mood and learning capacity can occur. Depression may be a consequence of long-term use and arthritic changes, frozen shoulder, and Dupuytren's contracture can be associated problems. Tolerance develops to the deleterious cognitive effects of the drug but also to its efficacy in some people. Phenobarbital is an enzyme inducer and can accelerate the metabolism of many lipid-soluble drugs and has an impact on bone health.

Piracetam

Piracetam is only indicated as an adjunctive treatment in refractory myoclonus. It has no use in other seizure types. The usual starting dose is 7.2 g daily in two or three divided doses, increased weekly by 4.8 g/day according to clinical response. Effective doses are usually between 12 and 24 g/day and this bulk is one of the limiting factors of the use of this drug. Piracetam is generally well tolerated. The commonest side effects are diarrhoea, weight gain, insomnia, and depression. Hyperkinesia has been reported with very high doses. There are no known drug interactions with piracetam.

Primidone

Primidone is metabolised to phenobarbital and its efficacy is similar to that of phenobarbital, but it is not as well tolerated. There is therefore nothing to recommend it over phenobarbital for people in whom treatment with a barbiturate is contemplated.

Sodium valproate (valproic acid)

Sodium valproate is a broad spectrum AED effective over the complete range of seizure types, with particular value in the idiopathic generalised epilepsies. Its use in women of childbearing potential, however, is problematic in view of its potential teratogenicity.

The starting dose of sodium valproate for adults and adolescents should be 500 mg/day for one or two weeks, increasing in most people to 500 mg twice daily. The controlled release formulation can be given once daily. Alterations thereafter should be made according to clinical need. Since the drug can take several weeks to become fully effective, frequent dosage adjustments shortly after initiating therapy may be unwarranted. As valproate does not exhibit a clear-cut concentration-effect-toxicity relationship and the daily variation in the level at a given dose is wide, routine monitoring is not helpful unless used as a check of adherence to therapy.

Side effects of sodium valproate include dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities including amenorrhoea. Polycystic ovarian syndrome has been reported in some women. Sedation is an uncommon complaint, although stupor and encephalopathy can occur, albeit rarely, possibly as a consequence of underlying carnitine deficiency. Hepatotoxicity, histologically a microvesicular steatosis similar to that found in Reye's syndrome, affects fewer than one in 20,000 exposed individuals. Children under three years of age receiving AED polypharmacy are the highest risk group. Mild hyperammonaemia without hepatic damage is seen in up to 10% of people taking it. This is usually transient, but occasionally can present clinically with confusion, nausea and vomiting and clouding of consciousness. Other sporadic problems include thrombocytopenia and pancreatitis. Valproate is far more teratogenic than other commonly used AEDs and this needs to be taken into account when treating women of childbearing age.

Sodium valproate can inhibit a range of hepatic metabolic processes, including oxidation, conjugation and epoxidation reactions. Targets include other AEDs, particularly phenytoin, phenobarbital, carbamazepine epoxide, and lamotrigine. Aspirin displaces sodium valproate from its binding sites on plasma protein and inhibits its metabolism. Sodium valproate, however, does not interfere with the hormonal components of the oral contraceptive pill.

Tiagabine

Tiagabine is last resort drug for focal seizures with or without secondary generalisation. It has no use in any other seizure type.

The recommended dose is between 30 and 45 mg/day, although higher doses (up to 80 mg/day) have been used. Tiagabine should be started at 10 mg/day in two divided doses, and increased by 5–10 mg/day each week up to 30 mg/day in the first instance. Doses above 30 mg/day should be given in three divided doses.

Tiagabine does not affect levels of carbamazepine or phenytoin, but may reduce the plasma concentration of valproate by about 10%, which is unlikely to be of clinical importance. Enzyme-inducing AEDs, however, decrease the half-life of tiagabine and people taking such drugs

as concomitant medication may need to take tiagabine three times a day from the beginning of treatment.

Side effects of tiagabine are primarily CNS-related and are more common during drug titration; the main side effects are sedation, headache, tiredness and dizziness. Tremor, diarrhoea, irritability, confusion, and depression are seen occasionally. Exacerbations of seizures and cases of non-convulsive status epilepticus have also been reported.

Topiramate

Topiramate is licensed as a first-line drug for people with focal seizures with or without secondary generalisation and for generalised seizure disorders.

Recommended doses are between 75 and 300 mg, although some people may derive benefit from a dose that is outside this range. The recommended starting dose for most people is 25 mg once daily, titrating upwards every two weeks in 25 mg/day increments up to 200 mg/day in two divided doses. After that, the dose can be increased by 50 mg each week until seizure control is achieved or side effects develop.

Topiramate exhibits linear pharmacokinetics with low levels of protein binding. It has minimal interaction with other AEDs, although hepatic enzyme inducers accelerate its metabolism. Because of this, topiramate doses may need to be adjusted downwards if people are coming off carbamazepine or phenytoin.

Most of the acute and dose-related side effects of topiramate are CNS-related including dizziness, drowsiness, headaches, irritability, cognitive slowing and speech impairment. These are usually transient and in some people seem to be related to the dose and rate of titration. Paraesthesia and nephrolithiasis have also been reported and are likely to be due to topiramate's carbonic anhydrase inhibitory action. People starting topiramate should increase their fluid intake to reduce the risk of kidney stones. Initial weight loss is seen in up to 40% of people and is usually not problematic. No idiosyncratic side effects have yet been described. Topiramate is teratogenic in some animal models and it is not recommended as a first-line option in women of childbearing potential.

Vigabatrin

Vigabatrin is now a last resort treatment for people with focal seizures. It is, however, still a first-line treatment for infantile spasms, particularly those associated with tuberous sclerosis. It has no use in primary generalised epilepsy and may worsen myoclonic seizures. Tolerance may develop in up to one-third of initial responders.

The recommended dose is 1000–2000 mg/day, although doses of up to 4000 mg/day in two divided doses can be used if necessary. Treatment should be started with a low dose (250–500 mg/day), and titrated slowly upwards over a period of several weeks until therapeutic response is achieved. Too rapid titration may be associated with an increased incidence of adverse events.

The addition of vigabatrin reduces plasma concentrations of phenytoin. The mechanism is unknown but may be due to decreased phenytoin absorption. Usually this has no clinical significance, but occasionally an increase in phenytoin dose is necessary if seizures increase a few weeks after the introduction of vigabatrin. The corollary of this effect is that plasma phenytoin concentrations rise after the withdrawal of concomitant vigabatrin therapy. Vigabatrin has no other known pharmacokinetic interactions. There is no need to measure the plasma concentration to guide dosing.

Sedation, dizziness and headache are the most commonly reported adverse effects, particularly when doses are being increased. Tolerance often develops and the symptoms are frequently self-limiting. These symptoms can usually be avoided by introducing the drug gradually. Allergic skin rashes are extremely rare. Up to 10% of people taking vigabatrin develop a change in mood, commonly agitation, ill temper and disturbed behaviour, depression or, more rarely, paranoid and psychotic symptoms. Visual field defects have been associated with long-term treatment with vigabatrin in up to 40–50% of people and this limits the use of the drug to those cases in which potential benefit outweighs risk.

CHAPTER 29

New antiepileptic drugs

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New antiepileptic drugs (AEDs) are necessary for people with chronic epilepsy and for improving upon established AEDs as first-line therapy. Since 2000, eleven new AEDs have been released in the UK. In chronological order these are: oxcarbazepine, levetiracetam, pregabalin, zonisamide, stiripentol, rufinamide, lacosamide, eslicarbazepine acetate, retigabine, perampanel and brivaracetam. Retigabine has had restrictions placed on its use because of association with skin and retinal pigmentary changes. Stiripentol and rufinamide, are licensed as orphan drugs for specific epileptic syndromes. Another drug, felbamate, is available in some EU countries. Their pharmacokinetic properties are listed in Table 1 and indications and a guide to dosing in adults and adolescents are given in Table 2. Known side effects are given in Table 3.

Complete freedom from seizures with the absence of side effects should be the ultimate aim of AED treatment and the new AEDs have not entirely lived up to expectations. Only a small number of people with chronic epilepsy have been rendered seizure free by the addition of new AEDs. Despite claims to the contrary, the safety profile of the new drugs is only slightly more favourable than that of the established drugs. The long-term side effect profile for the new drugs has also not yet been fully established.

New AEDs marketed in the UK*Brivaracetam*

Brivaracetam is an analogue of levetiracetam, and binds to the synaptic vesicle protein 2 (SV2) but with significantly greater affinity than levetiracetam. It is licensed for use as adjunctive therapy in focal seizures with and without secondary generalisation. Concomitant use of levetiracetam and brivaracetam is not recommended. Plasma levels of brivaracetam is reduced by co-administration of enzyme inducing drugs, but the clinical significance of this interaction is unknown. The adverse effect profile of brivaracetam, especially in comparison to levetiracetam remains to be fully established.

Eslicarbazepine acetate

Eslicarbazepine acetate is licensed as an add-on for focal epilepsy. It has similarities to carbamazepine and oxcarbazepine. As such it interacts with voltage-gated sodium channels and this is likely to be its main mode of action. There are no head-to-head comparisons between this drug and oxcarbazepine or carbamazepine but in the randomised clinical trial response was seen in some people that had not responded to carbamazepine or oxcarbazepine. Its tolerability and pharmacokinetic profile are similar to that of oxcarbazepine, although it may be associated with a lower risk of hyponatremia than oxcarbazepine.

Lacosamide

Lacosamide is licenced as an add-on for focal epilepsy in people over the age of 16 years. Its putative mode of action is not shared with any other currently available AEDs as it enhances

the slow inactivation of sodium channels. Dizziness is the commonest side effect. Co administration with other sodium channel blocking AEDs may worsen side effect profile.

Table 1. Pharmacokinetics of new antiepileptic drugs available in the UK.

Drug	Absorption (bioavailability)	Protein binding (% bound)	Elimination half-life(hours)	Route(s) of elimination
Brivaracetam	Rapid absorption (100%)	<20%	7-9	Urinary and hepatic
Eslicarbazepine	Rapid absorption	30-40	12-20	Urinary excretion
Levetiracetam	Rapid absorption (95-100%)	<10	7-12	Urinary excretion
Lacosamide	Rapid absorption	<15%	9-13	Urinary excretion
Oxcarbazepine	Rapid absorption (95-100%)	35-40	8-10	Hepatic metabolism Active metabolite
Perampanel	Rapid absorption	90-95%	70-80	Mainly hepatic metabolism
Pregabalin	Rapid absorption	<5	8-10	Urinary excretion
Retigabine	Rapid absorption	60-80%	8-11	Mainly urinary excretion
Zonisamide	Rapid absorption	40%	40-60	Urinary excretion

Table 3. Side effects of new antiepileptic drugs.

Side effects	Brivaracetam	Eslicarbazepine acetate	Levetiracetam	Oxcarbazepine	Lacosamide	Perampanel	Pregabalin	Retigabine [†]	Zonisamide
Dose related	*Tiredness, dizziness, *somnolence, irritability, depression, anxiety, insomnia, nausea, vomiting, suicidal ideation, aggression, agitation	*Fatigue *Drowsiness Diplopia Dizziness Hyponatraemia Ataxia Nausea Nystagmus Tremor	*Irritability *Depression Psychosis Headache Asthenia Ataxia Drowsiness	*Fatigue *Drowsiness *Diplopia *Dizziness *Hyponatraemia Ataxia Nausea Nystagmus Tremor	* Dizziness * Nausea * Headache * Lethargy * Diplopia	* Mood changes (suicidality) *Drowsiness *Ataxia *Lethargy *Blurred vision Irritability	*Dizziness Drowsiness Ataxia Weight gain Diplopia Tremor Abnormal thinking	*Drowsiness *Dizziness *Slurred speech *Ataxia Pigmentary changes	*Drowsiness Dizziness *Anorexia Concentration/Memory impairment Ataxia *Confusion Word-finding difficulties Agitation Depression
Idiosyncratic or chronic effects		Rash		Rash				Skin and retinal discoloration	Skin rash Blood dyscrasias

*Commonest side effects [†]Retigabine should only be prescribed when other appropriate drug combinations have proved inadequate or have not been tolerated

Table 2. Dosage guidelines for new antiepileptic drugs in adolescents and adults.

Drug	Indications	Starting dose	Standard maintenance dose	Dosage interval
Brivaracetam	Focal seizures	50 mg	100-200 mg	bid
Eslicarbazepine acetate	Focal seizures	400 mg	800-1200 mg	bid
Levetiracetam	Focal seizures, generalised seizures	500 mg	1500-3000 mg	bid
Lacosamide	Focal seizures	100 mg	200-400 mg	bid
Oxcarbazepine	Focal seizures	300-600 mg	1200-2400 mg	bid
Perampanel	Focal seizures	2 mg	4-10 mg	od or bid
Pregabalin	Focal seizures	100-150 mg	150-600 mg	bid
Retigabine[†]	Focal seizures	300 mg	450-900 mg	tds
Zonisamide	Focal seizures, generalised seizures	50 mg	200-600 mg	bid

[†]Retigabine should only be prescribed when other appropriate drug combinations have proved inadequate or have not been tolerated.

No drug-drug interactions are known but there are suggestions of pharmacodynamic interaction with traditional sodium channel blockers such as carbamazepine and oxcarbazepine.

Lacosamide commonest side effects are dizziness, headaches, nausea, and diplopia. It seems better tolerated if no traditional sodium channel blockers are used concomitantly. No idiosyncratic side effects have yet been associated with this drug. It should be used with caution in people with a history of cardiac conduction problems as it is known to increase the PR interval in some people.

Levetiracetam

Levetiracetam, a piracetam derivative, is a broad-spectrum drug indicated both as a first-line drug and as an add-on drug. Its mode of action is not fully understood. It has a binding site in the brain for which the natural ligand is the synaptic vesicle protein SV2A, but it is not known if this is related to its mode of action.

The recommended doses are between 1000 and 3000 mg/day divided into two doses although some people respond to doses outside this range. Levetiracetam should be started at 500 mg/day divided into two doses and increased by 250–500 mg/day every week up to 1000–1500 mg/day in the first instance.

Levetiracetam is well tolerated overall. Somnolence, dizziness, asthenia, ataxia, insomnia, behavioural problems (particularly irritability, usually of a transient nature) and mood changes are the most common side effects. No definite pharmacokinetic interactions have yet been identified. It appears not to be associated with increase in the rate of congenital malformations, and therefore would be appropriate.

Oxcarbazepine

Oxcarbazepine, the 10-keto analogue of carbamazepine, has a similar mechanism of action to carbamazepine. Its indications are very similar to those of carbamazepine; it is effective in focal seizures with or without secondary generalisation and may worsen absences and myoclonic seizures.

The recommended doses are between 600 and 2400 mg/day divided into two doses. Oxcarbazepine should be started at 300 mg/day and increased by 300 mg/day each week, up to 900 mg/day in the first instance.

Oxcarbazepine weakly induces hepatic enzymes, and so is likely to have fewer drug interactions than carbamazepine. A high dose of the oral contraceptive pill is advised to give protection against pregnancy. Oxcarbazepine exhibits less autoinduction than carbamazepine. Its safety profile is very similar to that of carbamazepine apart from hyponatraemia, which is more pronounced with oxcarbazepine and allergic skin reactions which are less common. Cross-sensitivity is seen in less than one-third of people hypersensitive to carbamazepine. There are indications of teratogenicity in animal models, particularly at high doses, but there is insufficient data from pregnancy registries to be certain about risk in human pregnancy.

Perampanel

Perampanel has been licenced for the adjunctive treatment of refractory focal epilepsy. It is the first licenced drug that interacts with glutamate receptors. Its effective dose is likely to be somewhere between 4 and 12 mg/day. No clinically significant pharmacokinetic interaction has yet been seen. It can be given in a once-a-day regimen, because of its long half-life.

The commonest treatment emerging events seen in trials were drowsiness, ataxia, lethargy, irritability, weight gain and blurred vision. In the post marketing phase, mood changes and suicidality has

become apparent in a small number of patients. Therefore, patients starting perampanel should be counselled regarding potential mood changes.

Pregabalin

Pregabalin has been licensed for the adjunctive treatment of refractory focal epilepsy. People with comorbid generalised anxiety seem to particularly benefit from it. Pregabalin is closely related to gabapentin, it is also a structural analogue of the neurotransmitter GABA that does not seem to affect transmitter response. It modulates calcium channels by binding to a subunit of Ca⁺ and this action is thought to be the basis of its antiepileptic mechanism.

The recommended dosages are between 150 and 600 mg divided into two doses, although some people may respond to doses outside this range. Pregabalin would normally be started at 50 or 75 mg bid and increased in incremental steps of 50 mg every two weeks up to 600 mg according to clinical need. Pregabalin is available in 25, 50, 75, 100, 150, 200 and 300 mg tablets.

Overall pregabalin is well tolerated and so far no idiosyncratic side effects have been described. Dizziness, drowsiness, ataxia, tremor and diplopia are the most common side effects. Weight gain, particularly with higher doses can be a major issue for some people. No pharmacokinetic interactions have yet been identified. In addition to its use in epilepsy, pregabalin has also been indicated for neuropathic pain and in generalised anxiety disorders.

Stiripentol

Stiripentol is licensed as an orphan drug for Dravet's syndrome when used in conjunction with sodium valproate and clobazam. It is an aromatic alcohol and is unrelated to any other AED. Its mode of action is unknown.

Retigabine

Retigabine was licensed as add-on for focal epilepsy in 2011. It is a modulator of neuronal voltage gated potassium channels. Recommended dosing is between 600 and 1200 mg a day. The commonest treatment emergent side effects are CNS-related and drowsiness, dizziness, slurred speech, ataxia, tremor and diplopia. It also causes urinary tract symptoms in some people. No clinically significant pharmacokinetic interaction has yet been seen.

Some patients taking retigabine for more than 2 years reportedly developed skin and retinal pigimentary changes, which in some cases was associated with decreased visual acuity. The Medicines & Healthcare products Regulatory Agency (MHRA) in the UK has designated retigabine as a drug of last resort, to be used where no alternative exists. Patients should receive counselling regarding ocular adverse effects and have baseline ophthalmological assessments, which will need to be repeated at 6 monthly intervals.

Rufinamide

Rufinamide is licensed as an orphan drug for the Lennox-Gastaut spectrum when used as an adjunctive. It is a triazole derivative and is unrelated to any other AED. Its mode of action is unknown.

Zonisamide

Zonisamide, a sulphonamide analogue which inhibits carbonic anhydrase, is a potent blocker of the spread of epileptic discharges. This is believed to be mediated through action at voltage-sensitive sodium channels. It is currently indicated for people with focal seizures with or without secondary generalisation, as well as in generalised epilepsies. It can be effective in generalised seizures particularly myoclonic seizures. Recommended doses are between 200 and 500 mg/day, although some people may derive benefit from doses outside this range. The recommended starting dose is 50 mg once daily (although in polytherapy 25mg OD may be improve tolerability),

titrating upwards every two weeks in 50 mg/day increments until seizure control is achieved or side effects develop. Its long elimination half-life allows once-daily dosing.

Zonisamide may increase phenytoin levels by about 10-15%. Zonisamide metabolism is induced by carbamazepine, barbiturates and phenytoin and higher doses may be necessary during co-administration with these AEDs.

Side effects include dizziness, drowsiness, headaches, hyporexia, nausea and vomiting, weight loss, skin rashes, irritability, impaired concentration and fatigue. These are mostly transient and seem to be related to the dose and rate of titration. Nephrolithiasis has also been reported, particularly in Caucasians, and patients should be advised to increase their fluid intake to reduce this risk. Its teratogenic potential remains unknown, and therefore is not recommended in pregnancy.

AEDs marketed elsewhere

Felbamate

Felbamate is a di-carbamate closely related to meprobamate. Its exact mechanism of action is not known. It is a drug with a broad spectrum of action but due to its safety profile it is used as a drug of last resort in people with intractable epilepsy, particularly in those within the Lennox-Gastaut spectrum. The usual dose is between 2400 and 4800 mg/day. The recommended starting dose for most people is 400 mg once daily, titrating upwards every week in 400 mg/day increments up to 2400 mg/day in two or three divided doses.

Felbamate exhibits significant pharmacokinetic interactions with phenytoin, carbamazepine and valproic acid: plasma phenytoin concentrations rise by 20% upon introduction of felbamate; plasma carbamazepine concentrations are reduced by 20-25% but there is a concurrent increase in the concentrations of 10,11-epoxy-carbamazepine, a metabolite of carbamazepine; plasma valproate concentrations increase by about 50% during co-medication with felbamate. The exact mechanism of these pharmacokinetic interactions is unknown but their magnitude requires dosage adjustments. Felbamate metabolism is also inducible by carbamazepine and phenytoin, and higher doses of felbamate may be necessary during co-administration with these AEDs.

The most frequently reported side effects during felbamate therapy have been neurological (diplopia, insomnia, dizziness, headache and ataxia), and gastrointestinal (anorexia, nausea and vomiting). The biggest concern is its potential to cause aplastic anaemia and liver failure, affecting as many as one in 3000 people exposed to the drug, which may be fatal. This has led to severe restrictions being placed on its use, and the drug is currently only available on a named patient basis.

Antiepileptic drugs currently in development

Cannabidiol

Cannabinoids have long been believed to have antiepileptic properties. The cannabis sativa plant has over 100 cannabinoids (phytocannabinoids), of which cannabidiol (CBD), a non-psychoactive phytocannabinoid, has been subjected to RCTs in Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS). Based on the results of these studies, the US FDA has licenced CBD for the treatment of DS and LGS. Marketing authorisation application has been made to the European Medicines Agency, and a decision is still awaited at the time of going to print. A small number of patients in the UK have been treated with CBD, as part of compassionate use and early access programmes. The licensing, commissioning and funding of CBD in the UK is yet to be clarified, and it will be several months before CBD is available to be prescribed in the UK. Many patients already use non-medicinal CBD, and it is likely that neurologists will come under increasing pressure to prescribe cannabis-based medications for a range of epilepsies, where evidence for efficacy and safety does not exist.

CHAPTER 30

Drug treatment of paediatric epilepsy

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Basic principles

Once the diagnosis of epilepsy and the epilepsy syndrome have been established (see also Chapter 23), there are a number of decisions which must be taken regarding the use of antiepileptic drugs (AEDs) (Table 1). Only the first four points in Table 1 will be discussed in this chapter.

The decision to treat a child with a drug depends upon the individual (frequency of seizures, epilepsy syndrome and neurological findings) and also the wishes of the parents/carers. It remains unclear when drug treatment should begin¹⁻³, and numerous attempts have been made to accurately predict the risk of epilepsy developing (i.e. recurrent, spontaneous seizures) after the first unprovoked seizure³. Nevertheless, the decision to treat- and when to treat remains- an individual one. Most clinicians would not recommend starting treatment after a single, brief generalised tonic-clonic seizure, but would after a cluster of seizures or, possibly, after an episode of unprovoked status epilepticus. Similarly, a child with severe physical and learning difficulties who develops infrequent myoclonic or generalised atypical absence or focal seizures may not necessarily require an AED. The recently published ILAE working definition of epilepsy takes these considerations into account⁴.

Table 1. Decisions regarding AEDs in children.

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- When to start a drug
 - Which drug and in what dose
 - When to change the drug
 - When (and how) to add a second drug (and which one)
 - When to seek a specialist opinion (paediatric neurologist)
 - When to stop the drug(s)
 - When to consider alternative therapies, including surgery
-

However, a child with normal intelligence who experiences frequent absence and generalised tonic-clonic seizures on waking may require treatment. Once a drug is started the objective is to achieve complete seizure control using a single drug, without causing side effects, and to use the most appropriate formulation to ensure that the child can actually take and absorb the medication.

The identification of the syndrome or seizure type provides information on the prognosis of the epilepsy and choice of AED. However, when prescribing for infants and young children the selection of the most appropriate AED must take into account the safety profile of that drug (i.e. the risk of and type of side effects) and also the available formulation of the drug.

This is particularly relevant in paediatric epilepsy where there is still a relative lack of knowledge and understanding about possible long-term effects of AEDs on growth and development, as well as concern about the short-term effects on behaviour, intellectual function and patterns of sleep. Although the newer AEDs appear to have a more acceptable safety profile, this optimism should remain somewhat guarded in view of the lack of any long-term data. Justification for this caution is derived from experience with felbamate where aplastic anaemia and hepatitis became manifest only a few years after its introduction in the early 1990s, and also with vigabatrin, where a characteristic bilateral visual field constriction was identified only ten years after introduction.

Once the most appropriate AED has been selected, this should be used alone (monotherapy) and in the lowest dose that controls the seizures without producing unacceptable side effects. This should be possible in approximately 70% of children. In children under the age of 12 years, dosages are usually based on bodyweight (mg/kg) rather than numbers of tablets/capsules (Table 2); this is clearly important in view of the wide age range of children treated and their different metabolic rates. For example, neonates, infants and children under the age of two frequently require relatively higher doses than older children and adolescents because of a higher rate of drug clearance.

When initial seizure control is suboptimal, or the AED has an obvious dose-response relationship, the dosage should be increased gradually until either seizure control is achieved or unacceptable side effects develop. If side effects occur before control is reached, the child will require either a different AED (substitute drug) or an additional AED (polytherapy). The choice of this second AED will depend upon the same criteria used to select the first but also on the likelihood of any potential interaction between the two drugs. How the change in AED therapy is effected depends on the child and the experience and beliefs of the clinician. If there has been some initial seizure control with the first AED it would be reasonable to add the next most appropriate AED, without withdrawing the first. If complete seizure control is then achieved, attempts to withdraw the first drug could be undertaken after a seizure-free period of between two and three months. If the initial AED has been wholly ineffective, it would seem logical to simultaneously replace the first drug with the second, thus maintaining monotherapy.

Polytherapy ('polypharmacy')

In some children, polytherapy with two AEDs is justified as this may result in additional (even complete) seizure control in another 10% of children. However, the problems of polytherapy include: pharmacodynamic interactions potentially reducing the effectiveness of each drug, difficulty in interpreting the effect of each drug, cumulative toxicity, and increased risk of idiosyncratic (allergic) toxic interactions. The decision regarding which additional AED to use is again dependent upon the seizure type/epilepsy syndrome and drug safety profile. Some authors term this 'rational polytherapy'. This 'rationalisation' may be determined theoretically by the drug's known (or postulated) mechanisms of action, or practically by following clinicians' experience of using certain drug combinations. Consideration must also be given to whether the two AEDs act synergistically or antagonistically, in terms of both effectiveness and safety. Examples of rational combinations

are shown in Table 3 (in part this reflects the authors' personal practice). The simultaneous use of three (or more) AEDs rarely, if ever, proves to be more effective than two drugs and will almost certainly result in increased side effects and, by causing drowsiness and disturbing a normal sleep pattern, may paradoxically exacerbate seizure control. Therefore, there needs to be an extremely good reason for using more than two drugs concurrently.

Table 2. Paediatric maintenance dosages of antiepileptic drugs.

Drug	Usual total daily dosage (mg/kg/day)	Doses/day
Acetazolamide	10-20	2
Carbamazepine	10-20	2/3 ¹
Clobazam	0.5-1.5	2
Clonazepam	0.1-0.3	2/3
Eslicarbazepine	15-30	2
Ethosuximide	15-35	2 (3)
Gabapentin	30-45	3
Lacosamide	2-8	2
Lamotrigine	(a) 2-5 ² (b) 4-10	2
Levetiracetam	30-50	2
Nitrazepam	0.5-1	2/3
Oxcarbazepine	20-30	2
Perampanel	8-10 (possibly 12) mg/day total	1
Phenobarbitone	4-8	2
Phenytoin	4-8 ³	2 (1)
Rufinamide	25-35 ⁴	2
Sodium valproate	20-40	2 ⁵
Stiripentol	25-35	2 (possibly 3)
Tiagabine	0.5-1.0	2/3
Topiramate	4-8 ⁶	2
Vigabatrin	50-100 ⁷	2
Zonisamide	4-5	2 (possibly 3)

1. The sustained release preparation (Tegretol Retard) may be given once or twice a day, depending on the timing of the seizures
2. Dose (a) is used when sodium valproate is being taken concurrently with lamotrigine; dose (b) is used with lamotrigine monotherapy or with drugs other than valproate
3. Dose varies considerably depending on age; neonates frequently require total daily doses in excess of 10-15 mg/kg
4. When used with sodium valproate the total daily dose is usually 20-25 mg/kg in children with a body weight of <30 kg; titration to the maintenance dose also takes slightly longer
5. The sustained release preparation (Epilem Chrono) is usually given once a day
6. The starting dose should be 0.5 mg/kg/day
7. When treating partial seizures, the usual maintenance dose is usually 30-50 mg/kg/day. When treating infantile spasms, the usual dose is 80-100 mg/kg/day although lower doses may be effective; the maximum dose is 120-150 mg/kg/day

Also, it is unlikely that polytherapy with three AEDs will produce any additional, significant and sustained control; however, polytherapy using three or more drugs will almost certainly be associated with an increased risk and frequency of side effects, as well as toxicity due to drug interactions. The only situation where three drugs are acceptable is during substitution, i.e. one

drug being introduced as another is withdrawn or where a medication is seen to have a main affect with one other, for example stiripentol. Unfortunately, it is usually far easier to initiate polytherapy than to terminate it.

It is tempting but perhaps rather naïve to expect that any of the new AEDs, with recognised and even ‘designed’ mechanisms of action, will necessarily offer a more rational or scientific basis for using specific drug combinations in every patient.

Drugs available

The older and most commonly used medications in the treatment of childhood epilepsy are sodium valproate and carbamazepine. Phenytoin and phenobarbitone, previously drugs of first choice for most seizure types before the advent of carbamazepine and sodium valproate, are no longer considered to be first, second or third-line drugs because of their relatively unsatisfactory long-term safety profile. However, in certain situations they may still be effective, but only when other drugs have ‘failed’ and where seizure control is the major - if not only - priority. Further, they remain the first-line treatment in the acute management of neonatal seizures in view of their parenteral availability and safety profile.

Although sodium valproate can be utilised in girls under 10 years, consideration needs to be given as to whether it will be required in the longer term, as it can no longer be first line in girls of child bearing potential. Should it be utilised, MHRA guidance needs to be considered and the girls be on a clear pregnancy prevention plan, in view of the risk to the unborn child (<https://www.gov.uk/guidance/valproate-use-by-women-and-girls>).

The benzodiazepines⁵ are also effective AEDs, particularly for generalised, but also for focal seizures and some epilepsy syndromes. Their use may be restricted by acute toxicity, and the development of tolerance or tachyphylaxis. For these reasons, benzodiazepines are rarely, if ever, the initial AED, other than for infants and children with myoclonic seizures as the only seizure type, when low-dose clonazepam or clobazam may be used as monotherapy. Nitrazepam may be effective in suppressing infantile spasms, and particularly when these have arisen as a consequence of neonatal hypoxic-ischaemic encephalopathy. Clobazam is also often very effective as an add-on treatment for treating partial seizures (with or without bilateral convulsive seizures), atypical absences, electrical status epilepticus of slow-wave sleep (ESESS) and catamenial seizures. Ethosuximide has traditionally been used for childhood absence epilepsy, but can also be effective where spike-wave activity is prominent, such as atypical absence of Lennox-Gastaut syndrome or continuous spike-wave of slow sleep.

Numerous AEDs are licensed for use in the UK as ‘add-on’ (adjunctive) or as monotherapy in a range of seizure types and epilepsy syndromes – vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, zonisamide, rufinamide, lacosamide, eslicarbazepine and perampanel. Lamotrigine has a monotherapy licence for patients aged 12 years and older but as adjunctive therapy from two years. Vigabatrin has a monotherapy licence for use in the management of children with infantile spasms (West syndrome) in the UK. Topiramate now has a licence for use as monotherapy in children aged six years and above. The licence for levetiracetam is currently as monotherapy for patients aged four years and above; this drug also has a licence as adjunctive therapy for treating focal seizures from one month of age and myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy (JME). Pregabalin, zonisamide and lacosamide have licences for use as adjunctive therapy in people aged 18 years and above. Perampanel has a license for adjunctive therapy of focal seizures over the age of 12 years. Of these new AEDs, lamotrigine, topiramate and levetiracetam would appear to have the broadest spectrum of action, being effective against many generalised and focal seizure

types, and relatively free of serious side effects, other than lamotrigine producing an allergic or idiosyncratic rash, that rarely develops into Stevens-Johnson syndrome^{7,8}. Lamotrigine can be effective in controlling typical absence seizures⁹ but not as effective in suppressing myoclonic seizures. Levetiracetam also has a broad spectrum of action against different seizure types and its safety profile would appear to be relatively impressive, with hostility/aggression as the only significant and possibly drug-limiting side effects.

Table 3. Drugs of first and second choice in the treatment of various seizure types and epilepsy syndromes, and drugs to avoid in view of risk of exacerbation of seizures. (Adapted from NICE¹²)

Seizure type/syndrome	First line	Adjunctive AEDs	Do not offer (may worsen seizures)
Focal seizures	CBZ, LTG, OXC, TPM, VPA	CLB, GBP, LEV, PHT, TGB	
Generalised seizures	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Absence			
GTC	CBZ, LTG, OXC VPA,	CLB, LTG, LEV, VPA, TPM	(if absence or myoclonic seizures) CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Myoclonic	LEV, VPA, TPM	LEV, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Tonic or atonic	VPA	LTG	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Childhood absence epilepsy or other absence syndromes	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Juvenile absence epilepsy or other absence epilepsy syndromes	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Juvenile myoclonic epilepsy	LTG, LEV, VPA, TPM	LTG, LEV, VPA, TPM	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Genetic generalised epilepsy	LTG, VPA, TPM	LTG, LEV, VPA, TPM	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
BECTS	CBZ, LTG, LEV, OXC, VPA	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	
Panayiotopoulos syndrome	CBZ, LTG, LEV, OXC, VPA	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	
Late-onset childhood occipital epilepsy (Gastaut type)	CBZ, LTG, LEV, OXC	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	

Table 3. Continued

Seizure type/syndrome	First line	Adjunctive AEDs	Do not offer (may worsen seizures)
Infantile spasms not due to tuberous sclerosis	Discuss with or refer to a tertiary paediatric epilepsy specialist Steroid (prednisolone or tetracosactide) or VGB		
Dravet syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist VPA, TPM	CLB, stiripentol	CBZ, GBP, LTG, OXC, PHT, PGB, TGB, VGB
Lennox-Gastaut syndrome	Discuss with or refer to a tertiary paediatric epilepsy specialist VPA	LTG	CBZ, GBP, OXC, PGB, TGB, VGB
Landau-Kleffner syndrome	Refer to a tertiary paediatric epilepsy specialist Steroids, LTG, VPA		
Continuous spike-wave in slow sleep	Refer to a tertiary paediatric epilepsy specialist Steroids, CLB, VPA, LTG, ESM	LEV, TPM	CBZ, OXC, VGB
Myoclonic-astatic epilepsy	Refer to a tertiary paediatric epilepsy specialist VPA, LEV	LTG, TPM	CBZ, OXC

CBZ carbamazepine; CLB clobazam; CLN clonazepam; ESM ethosuximide; GBP gabapentin; LEV levetiracetam; LTG lamotrigine; OXC oxcarbazepine; PHT phenytoin; VPA sodium valproate; TGB tiagabine; TPM topiramate; VGB vigabatrin

Vigabatrin is also a very effective drug in the treatment of infantile spasms¹⁰ to the point where it is recognised as a drug of first choice^{11,12}, particularly when the underlying cause is tuberous sclerosis¹³⁻¹⁵. Vigabatrin is also useful for focal seizures, with or without bilateral convulsive seizures, and appears to be particularly effective in children who have an underlying structural lesion such as focal cortical dysplasia or even low-grade tumours. However, the drug may exacerbate myoclonic

and typical absence seizures¹⁶⁻²⁰. The drug also appears to have a relatively impressive short-term safety profile. Rarely, however, behavioural effects may occur, which manifest as either agitation or a change in muscle tone and an increased appetite; these effects are transient and resolve once the dose is reduced or the drug withdrawn. However, the peripheral visual field constriction reported to occur in up to 40% of adult patients treated with vigabatrin²¹ is clearly of concern and, consequently, this drug is now only rarely (possibly never) prescribed to adults or older children for focal seizures. At the current time, visual field defects have been reported in children but it is not known whether children are likely to be at a higher or lower risk of developing a visual field defect and also whether any visual field constriction is more or less likely to be reversible than in adults. The reported incidence is 20-25% and has been derived from older children treated with this drug for focal seizures but this figure may be higher or lower because it is often very difficult to accurately obtain formal visual field assessment (perimetry) in children with a cognitive age of <9 years. Limited data also suggest the occurrence to be related to dose and duration of treatment²². The drug should only be prescribed in children after careful consideration of the risk:benefit ratio.

Efficacy and safety data on the use of gabapentin in children are limited, although it does appear to be effective in focal seizures²³⁻²⁵. Of all the new AEDs, gabapentin appears to be the least potent in treating focal seizures in children and the one with the lowest chance of rendering children seizure free²⁴. In adults the drug is effective in focal seizures with and without evolution to bilateral convulsive seizures^{26,27}; there is little information on generalised tonic-clonic seizures, although it would appear to have no effect (beneficial or detrimental) in typical absences²⁸. Adverse events appear to be both mild and infrequent with gabapentin, and there are no known drug interactions. Unfortunately, it often has to be administered three times a day (which has implications for some school children), and as yet there is only a capsule formulation that restricts its use in children. A 'mixed fruit'-flavoured suspension is available in the US.

Topiramate is effective in focal onset seizures and also in the Lennox-Gastaut syndrome²⁹⁻³³ (tonic and atonic seizures seem to respond best). Topiramate may also be effective as monotherapy in both focal and primary generalised tonic-clonic seizures³⁴ and also in treating Dravet syndrome. The drug does appear to be associated with a number of acute and predominantly dose-related side effects, particularly on the central nervous system. These include dizziness, drowsiness, irritability, 'fatigue', word-finding difficulties/mild cognitive impairment and, rarely, acute depressive and psychotic illness. These can be minimised by slow introduction. Paraesthesiae, renal calculi and glaucoma have also been reported but predominantly in adults; theoretically there is an increased incidence of renal calculi if children are receiving a combination of either topiramate and zonisamide or topiramate with the ketogenic diet over a long period (in excess of 12 or 18 months). Insomnia, anorexia and weight loss are additional reported side effects with topiramate³⁴.

There are few randomised clinical data on the use of tiagabine³⁴ in children. As with all new AEDs, the drug has been shown to be more effective than placebo in suppressing focal onset seizures in adults and some adolescents, without apparently causing any severe adverse effects^{35,36}. Like vigabatrin, tiagabine also has a direct effect on GABA-ergic neurotransmission (and GABA levels) and although it is theoretically possible that tiagabine might also affect visual field function, reports suggest that this drug does not produce the same visual field defect that is seen with vigabatrin. A number of anecdotal reports have suggested that the drug may precipitate non-convulsive status epilepticus^{37,38}.

Oxcarbazepine, structurally similar to carbamazepine, was licensed for use in the UK in 2002. Its spectrum of action is almost identical to carbamazepine, but by not being metabolised to the 11-epoxide metabolite it is associated with fewer adverse side effects than carbamazepine (i.e. less ataxia, diplopia and nausea). However, hyponatraemia is reported to occur more frequently with oxcarbazepine – although rarely with any significant clinical effects. The drug is available

as a standard (not slow or sustained) release tablet and liquid suspension. Finally, there is some evidence that oxcarbazepine will not be complicated by an idiosyncratic rash, even if the child has previously developed a rash with carbamazepine. Like carbamazepine, oxcarbazepine may exacerbate the absence and myoclonic seizures that occur in the generalised epilepsies³⁹.

There is a clear dose-response relationship with lamotrigine, gabapentin, topiramate, levetiracetam and probably pregabalin, tiagabine and zonisamide but not with vigabatrin³⁹, and none appear to be associated with either significant tolerance or tachyphylaxis. Finally, there is as yet no established plasma 'therapeutic range' for these new drugs; and as there is no correlation between plasma levels of vigabatrin and its clinical efficacy (due to its pharmacokinetic properties), such measurements are not helpful as a guide to dosage. Whether a random level can be usefully used to ascertain compliance remains to be determined – although this is probably useful where major non-compliance is possible.

Until 1994/5 felbamate was available in the UK on a compassionate, named-patient basis. Early reports from the US had suggested that it was effective for focal seizures in adults^{40,41} and generalised seizures associated with the Lennox-Gastaut syndrome in children⁴³. Unfortunately, a large number of patients developed aplastic anaemia, some with a fatal outcome. A severe, presumed idiosyncratic, hepatitis has also been reported. As a result of these serious adverse reactions, the drug is only available in the UK on a limited named-patient basis. However, in the US, the prescribing of felbamate continues to increase (slowly), but obviously with close monitoring of haematological and hepatic function. This re-emergence of felbamate has not been reported to be accompanied by a corresponding increase in additional cases of aplastic anaemia or hepatitis.

Zonisamide appears to have a broad spectrum of action, if data from Japan and the USA (where the drug has been used for over a decade) are to be believed, with reported benefits in treating patients with drug-resistant focal seizures, primary generalised tonic-clonic seizures, refractory myoclonic and absence seizures and even refractory infantile spasms^{44,45}. Its mechanism of action, and therefore its reported adverse side effects, appears to be similar, but less severe, to that of topiramate. Currently, in the UK, the drug only has a licence as an add-on treatment for treating focal seizures in patients aged 18 years and above; however, it is expected to receive a paediatric licence as adjunctive therapy within the near future (2013/14).

Rufinamide is licensed in the UK for treatment of seizures associated with Lennox-Gastaut syndrome. A randomised double-blind placebo-controlled trial of 139 participants aged 4–30 years showed significant benefit in most seizure types, particularly atonic ('drop') and absence seizures⁴⁶.

Cannabidiol, in its pure form with no THC as produced as a pharmaceutical by GW Pharma, has been trialled with positive data available as add on therapy in Dravet⁴⁷ and Lennox Gastaut syndromes^{48,49}. It has been licenced for use as add-on therapy in the USA; it has recently been assessed and given a positive decision if used in conjunction with clobazam by the EMA. Further assessment by NICE is ongoing. This is not the same as hemp oils as purchased from health food shops, which have no quality assurance as to content. Further there is no current evidence to suggest additional tetrahydrocannabinol (the part of the cannabis plant that is more likely to have cognitive effects) is required.

Many other drugs have been used in paediatric epilepsy, usually in an attempt to control multiple and refractory seizure types. Acetazolamide, a diuretic and carbonic anhydrase inhibitor, is considered by many to be a useful add-on drug (usually in combination with carbamazepine) in treating focal seizures⁵⁰. Pyridoxine (vitamin B₆) is clearly the treatment of choice in the rare inherited disorder of pyridoxine-dependent seizures⁵¹, but it has also been used in West syndrome (infantile spasms)⁵². A three-week trial of oral pyridoxine should also be used in any child under 18 months of age with

frequent seizures (including infantile spasms) that have been resistant to 'conventional' AEDs. If there has been no obvious or sustained response to pyridoxine, and there remains a high suspicion of pyridoxine-dependent epilepsy, the child should then receive a three- or four-week course of pyridoxal phosphate. Biotin should also be used in infants and young children with refractory seizures pending the result of a serum biotinidase level. Folinic acid should also be used for any infant with neonatal-onset seizures that have been resistant to both conventional antiepileptic medication and pyridoxine and where no cause has been found for the epilepsy.

The high-fat, low-carbohydrate ketogenic diet is a historical treatment that has gained more credibility as an effective management of children with drug resistant epilepsy⁵³. A randomised controlled trial has demonstrated definitive efficacy over no change in treatment. More relaxed forms of the diet have raised the possibility of it being available to use over a wide age range.

Steroids, given either as prednisolone or less commonly hydrocortisone or adrenocorticotrophic hormone (ACTH)⁵⁴ (this drug is no longer available in the UK and has been replaced by the synthetic steroid, tetracosactide, see Chapter 23), are frequently used in treating different seizure types or epilepsy syndromes, including acute epileptic encephalopathies. The mechanism of action of steroids is unclear but they may be very effective, particularly in the following situations:

- infantile spasms (West syndrome)
- continuous spike-wave in slow sleep (CSWSS), also called electrical status epilepticus of slow sleep (ESESS)
- Dravet syndrome
- Lennox-Gastaut syndrome, particularly in non-convulsive (atypical absence) status
- other, rare epileptic encephalopathies.

Intravenous immunoglobulins have been used with varying (usually very limited), success in intractable epilepsies including children with both the West^{55,56} and Lennox-Gastaut syndromes^{57,58}. There are marked variations in the frequency of courses, duration of treatment and doses of this particular therapy and there is as yet no established or universally accepted mechanism of action.

Which drug?

Drug choice in childhood epilepsy should, wherever possible, be evidence based as in older individuals. However, there are few randomised controlled trials on which to base drug choice within the epilepsy syndromes. This in part reflects the logistical and ethical difficulties as well as the expense in conducting paediatric trials. Nevertheless, the principal should still be to try and base treatment strategies on robust evidence. The EMA has recently revised guidelines on the development of AEDs in children. They state that focal epilepsies in children older than four years of age have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children, provided the appropriate dose and safety data are established. In children under four years of age, short-term assessment of response by using video-EEG monitoring may be sufficient once efficacy has been demonstrated in older children. For syndromes limited to childhood, sufficient experience needs to be gained in this population before a new medicinal product may be registered for these indications in children⁵⁹; predictably such experience is likely to be largely anecdotal unless data can be obtained from well-conducted national or international randomised controlled trials.

Many studies are conducted on the basis of seizure type rather than syndrome, are limited in duration and reveal little in the way of long-term effects. The HTA (in 2004) suggested that older drugs such as sodium valproate or carbamazepine should be used as first line over and above newer anticonvulsants unless there was a contraindication⁶⁰. The NICE guidelines for the diagnosis and management of epilepsy in primary and secondary care, originally published in 2004, underwent a pharmacological review in 2012¹². These took a GRADE approach to evaluating evidence and guidance produced was based also on the cost effectiveness of AED use. A further update of the guidelines is due to be published in 2021.

Many paediatric epilepsies and epilepsy syndromes are associated with generalised seizures, and for these the current drug of choice (at least in the UK) is usually sodium valproate. This was confirmed by the SANAD (Standard and New Antiepileptic Drugs) study, which showed sodium valproate to be superior in the treatment of generalised seizures over topiramate and lamotrigine where sodium valproate would have been the physicians' choice (arm B). Many of the individuals in this study had genetic generalised epilepsy⁶¹. Further, a recent randomised double-blind trial in the treatment of childhood absence epilepsy comparing ethosuximide, sodium valproate and lamotrigine showed superior efficacy of sodium valproate and ethosuximide over lamotrigine, but some neuropsychological advantage to ethosuximide⁶². There has been increasing concern about the effect of sodium valproate on the unborn child of mothers taking the medication – both an increased risk of malformations, as well as cognitive delay in later childhood. For this reason, the medication is not recommended as first line in girls of child-bearing age, and when considered, the risks of taking the medication need to be weighed against the risk of the epilepsy itself in each individual and the MHRA guidance followed.

Epilepsies associated with focal seizures are slightly less common in children in contrast to adults and for these individuals carbamazepine is the usual preferred treatment. Data from the SANAD study⁶³ arm A where carbamazepine would have been physicians' choice demonstrated that lamotrigine was at least as effective and associated with fewer adverse side effects than carbamazepine, oxcarbazepine, topiramate and gabapentin. Although SANAD was inclusive of children in the protocol, few children were recruited to this arm, and in the majority those included had symptomatic focal epilepsy, which is less common than idiopathic focal epilepsy in children.

One major syndrome to consider is West syndrome, characterised by infantile spasms and hypsarrhythmia on EEG; most, but not all children also demonstrate developmental plateau or even regression, particularly if the diagnosis is delayed. It is recommended that hormonal treatments (ACTH, tetracosactide or prednisolone) or vigabatrin should be used as first-line monotherapy drugs in treating infantile spasms^{11,12}. Vigabatrin is particularly effective in treating infantile spasms caused by tuberous sclerosis¹² but appears to be slightly less effective than tetracosactide or prednisolone in treating spasms due to other aetiologies^{64,65}. However, there are currently differences of opinion regarding the treatment of infantile spasms, in part reflecting clinicians' concerns over drug safety and in part availability of medication. In the US, ACTH or prednisolone is the preferred treatment⁶⁴; until recently vigabatrin has not been freely available, whereas in many European countries vigabatrin is widely used. A more recent study, the International Collaborative Infantile Spasm Study (ICISS), highlighted that short term response is more likely with vigabatrin steroid combination therapy than steroids alone⁶⁶. Which is used will depend on family and physician choice, weighing up the risk:benefit of the treatment involved. Although use of vigabatrin in adults and older children has been associated with visual field constriction, this appears to be related to dose and duration of treatment²¹ and does not necessarily prevent or reduce the use of this drug in treating infantile spasms when weighed up against the risk of short-term high-dose steroids.

In Dravet syndrome, medications of choice are sodium valproate, clobazam and topiramate. Furthermore, a well-constructed randomised crossover study demonstrated stiripentol,

a cytochrome P450 inhibitor, to be significantly more effective than placebo when added to sodium valproate and clobazam⁶⁷. More recently trials have shown cannabidiol to be a further effective agent. In addition, a previously used appetite suppression, fenfluramine, has been specifically shown to be extremely effective in this syndrome with no current evidence of the cardiac effects originally leading to the medication becoming not available⁶⁸. Assessment by the EMA and FDA are ongoing. Of greater note is the observation that medications acting on sodium channels (e.g. lamotrigine, phenytoin) may cause aggravation of seizures in this syndrome^{69,70} and therefore should be avoided.

Several studies have been conducted evaluating treatments against placebo in Lennox-Gastaut syndrome as add-on therapy. A Cochrane Review was able to evaluate seven randomised controlled trials. All but two studies evaluated different therapies. Overall the authors concluded that no study to date had shown any one drug to be effective over and above another but lamotrigine, rufinamide, clobazam, topiramate and felbamate may be helpful as add-on therapy⁷¹. There are also RCTs demonstrating effectiveness of cannabidiol compared to placebo. Until further research has been undertaken clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.

There is still probably a clear need for novel AEDs in childhood epilepsy. These must be effective (preferably with a broad spectrum of action against a wide range of seizure types), safe and be available in child-friendly formulation. However, while the advent of the new AEDs should be welcomed, it is important to use the older, 'conventional' AEDs appropriately and initially, particularly in view of the limited data on both monotherapy efficacy and long-term safety for newer compounds. In this regard, it is common for a child to be falsely described as being refractory to treatment because they have been prescribed the wrong drug for their epilepsy syndrome. The classic example is the use of carbamazepine or oxcarbazepine for juvenile-onset absence or juvenile myoclonic epilepsy, when it is known to exacerbate both the myoclonic and absence seizures which characterise these syndromes. Further, when initiating teenage girls on medication that may need to be lifelong, the possibility of pregnancy and the effects of AEDs in utero need to be taken into consideration and individuals counselled accordingly; this is particularly important when discussing and prescribing sodium valproate.

With the advent of increasing genetic diagnoses, particularly in the early onset more complex epilepsies, there is the real possibility of understanding the underlying pathophysiology, and for considering the underlying cause in considering treatment. An understanding of the genetic pathway may lead to a rethink of treatment, e.g. mTOR inhibitors in TSC disease, and even repurposing of medications e.g. quinine in KCNT1 mutations. Further, the understanding of gain of function rather than loss of function mutations may lead to some existent medications being the treatment of choice e.g. sodium channel blockers in SCN8A mutations. This leads to the possibility of treatment beyond the seizures. This area will continue to evolve in the coming years, with personalised treatment a real possibility.

Summary and conclusions

- The choice of AED in treating the childhood epilepsies will be determined by the epilepsy syndrome (and therefore the specific seizures that help to define the syndrome), safety profile and, to a slightly lesser extent, its ease of use (formulation and dosing regimen)
- Sodium valproate appears to remain the most effective AED in treating generalised seizures, but should not be considered first line in girls of child bearing potential

- Lamotrigine, closely followed by carbamazepine or oxcarbazepine, appears to be the most effective and 'best tolerated' AED in treating focal seizures
- The major benefit of the newer AEDs seems to be their lower (and also milder) incidence of adverse side effects although there are some exceptions
- It is important to be aware of drugs that may exacerbate some seizure types
- The temptation should be strongly resisted to indulge in polypharmacy; it is always easier to add another drug than to withdraw one. There are no convincing data that the simultaneous use of three AEDs results in better seizure control than two drugs. 'Polypharmacy' increases the risk and incidence of adverse side effects; in addition, three drugs, in causing drowsiness and disturbing sleep patterns, may paradoxically cause a deterioration in seizure control, as well as an increase in adverse side effects. Consequently the prescribing mantra must be 'if I add, what can I take away' to avoid dangerous polypharmacy.

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CHAPTER 31

Pharmacokinetic interactions between antiepileptic drugs

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Classically, a drug interaction is regarded as a modification of the effect of one drug by prior or concomitant administration of another. Interactions can be divided into two broad types namely pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions occur as a consequence of an effect at the site of drug absorption, plasma protein binding, metabolism or elimination and are associated with changes in blood concentrations (levels). Pharmacodynamic interactions occur as a consequence of an effect at the site of action of a drug, are not associated with any change in blood concentrations and are concluded by default.

Commonly, drug interactions have been discovered as a result of unexpected changes in the clinical status of patients upon addition or withdrawal of a drug from existing medication. A clinically significant drug interaction can be defined as one that results in the need to adjust dosage regimens in the majority of patients. However, the end result in individual patients needs also to be considered. For example, a modest or even marked elevation of a low plasma antiepileptic drug (AED) concentration consequent to an interaction may merely improve seizure control, and a small elevation of a nearly toxic concentration may precipitate toxicity. Similarly, a marked interaction in an unusually susceptible individual receiving drug polytherapy that causes little change in the majority of patients is equally significant.

Table 1 shows the various AEDs the expected changes in plasma concentrations when an AED is added to a concomitant AED regimen.

The pharmacokinetic interactions that are most significant clinically can be attributed to interactions at the metabolic level, and the best examples relate to inhibition or induction of the hepatic monooxygenase enzyme system (cytochrome P450, CYP) involved in drug metabolism. Induction involves the synthesis of new enzyme, and requires protein synthesis. Consequently, it may take many days before induction is complete and results in an increased drug metabolism, reduced plasma concentrations and an attenuated pharmacological effect (if no active metabolite is present). The process goes in reverse when the inducer is withdrawn with an increase in plasma concentrations of the target drug and hence an increased potential for toxic side effects.

Commonly, inhibition results from competition between drugs for the same active site on an isoenzyme of CYP, while induction involves production of more isoenzyme and therefore more binding sites. Circulating concentrations of the inhibited drug increase to a new steady state between four and six half-lives after the interaction has begun. Consequently, potential pharmacological effects will occur quickly if a drug has a short half-life and more slowly if it has a long half-life. The minimum elapsed-time for maximum potentiation is; carbamazepine 4 days, ethosuximide 12 days, phenytoin 14 days, phenobarbitone 20 days, and valproate 3 days.

Table 1. Interactions between antiepileptic drugs (AEDs): Expected changes in plasma concentrations (levels) when an AED is added to a pre-existing AED regimen.

	PRE-EXISTING AED											PRE-EXISTING AED												
	CBZ	CLB	CZP	ESL-a	ESM	FBM	GBP	LCM	LTG	LEV	OXC	PMP	PB	PHT	PGB	PRM	RFN	STP	TGB	TPM	VPA	VGB	ZNS	
CBZ	AI	CLB DMCLB	CZP	ESL	ESM	FBM			LTG	LEV	H-OXC	PMP		PHT	PB	PRM	RFN	STP	TGB	TPM	VPA		ZNS	
CLB	CBZ CBZ-E	—	NA		NA	NA	NA	NA						PHT	NA	PRM		STP	?	NA	VPA	NA	NA	
CZP		NA	—	NA	NA		NA	NA			NA			PHT	NA		NA	NA	?	NA			NA	
ESL-a			NA	—	NA	NA		NA	LTG		NCCP	?		PHT	NA	?	NA	NA	NA	TPM	VPA	NA	?	
ESM		NA	NA	NA	—	NA	NA	NA			NA	?			NA	PRM	NA	NA	NA	NA	VPA	NA	NA	
FBM	CBZ CBZ-E	CLB DMCLB	CZP	?	?	—	NA	NA	LTG			?	PB	PHT	NA	?	?	?	?	?	VPA	VGB	NA	
GBP		NA	NA		NA	FBM	—	NA			NA	NA			PGB	NA		NA	NA			NA	NA	
LCM		NA		NA	NA	NA		—			H-OXC	?	NA		NA	NA	NA	NA	NA				NA	
LTG			CZP				NA		—	LEV								NA	NA		VPA	NA		
LEV						NA				—	NA						NA	NA	NA				NA	
OXC	CBZ	?	?	NCCP	?	?	NA		LTG	LEV	—	PMP	PB	PHT	NA	?	RFN	?	?	TPM		NA	NA	
PMP	CBZ	CLB		?	?	?	NA	NA	LTG		OXC**	—			NA	?	?	?	?		VPA	NA		
PB	CBZ	CLB DMCLB	CZP	?	ESM			LCM	LTG	LEV	H-OXC		AI	PHT		NCCP	RFN	STP	TGB	TPM	VPA		ZNS	
PHT	CBZ	CLB DMCLB	CZP	ESL	ESM	FBM		LCM	LTG	LEV	H-OXC	PMP	PB	AI	PGB	PB	PRM	RFN	STP	TGB	TPM	VPA	ZNS	
PGB		NA	NA	NA	NA	NA		NA			NA	NA			—	NA	NA	NA	TGB			NA	NA	
PRM	CBZ	?	CZP	?	ESM	?	NA	?	LTG		?	?	NCCP		NA	—	RFN	STP	TGB	TPM	VPA		ZNS	
RFN	CBZ		NA	NA	NA	NA	NA	NA	LTG	NA	NA	?	PB	PHT	NA	NA	—	NA	NA			NA	NA	
STP	CBZ	CLB DMCLB	?	?	ESM	?	NA	NA	?	NA	?	?	PB	PHT	NA	PRM	?	—	?	?	VPA	NA	?	
TGB		NA	NA	NA	NA	NA	NA	NA			NA	NA	NA		NA	NA	NA	NA	NA	—	NA	VPA	NA	NA
TPM		?	?	ESL	NA	?	NA					PMP		PHT				NA	?	—	VPA	NA	NA	
VPA	CBZ-E		?		ESM	FBM			LTG				PB	PHT *		PB	RFN			TPM	—			
VGB	CBZ	NA	NA	NA	NA		NA	NA			NA	NA		PHT	NA	NA	RFN	NA	NA	NA		—	NA	
ZNS	CBZ-E	?	?	NA	?	?	NA	NA		NA	?	?			NA		?	?	NA	NA		NA	—	

CBZ = carbamazepine; CBZ-E = carbamazepine-10,11-epoxide (active metabolite of CBZ); CLB = clobazam; CZP= clonazepam; DMCLB = N-desmethyloclobazam (active metabolite of CLB); ESLa = eslicarbazepine acetate; ESL = eslicarbazepine (active metabolite of ESL-a); ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; H-OXC = 10-hydroxy-oxcarbazepine (active metabolite of OXC); LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PGB = pregabalin; PRM = primidone; RFN = rufinamide; STP stiripentol; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; VGB = vigabatrin; ZNS = zonisamide. AI = autoinduction; NA = none anticipated; NCCP = not commonly co-prescribed;

= No change; = a usually minor (or inconsistent) decrease in plasma level; = a usually clinically significant decrease in plasma level; = a usually minor (or inconsistent) increase in plasma level; = a usually clinically significant increase in plasma level. * = free (pharmacologically active) level may increase; ** = the effect of the active metabolite H-OXC is not known; ? = unknown, an interaction could occur

Of the AEDs illustrated in Tables I, four (carbamazepine, phenytoin, primidone and phenobarbital) are potent enzyme inducers. Valproate and stiripentol are potent inhibitors. Phenytoin has some rather unique characteristics in that in addition to being an enzyme inducer, it is only loosely bound to CYP isoenzymes. It also exhibits saturation metabolic characteristics making it particularly susceptible to inhibitory interactions. Of the newly licensed AEDs, gabapentin, lacosamide, levetiracetam, pregabalin and vigabatrin uniquely do not appear to affect the concentrations of other AEDs. In contrast eslicarbazepine acetate, lamotrigine, felbamate, oxcarbazepine, tiagabine, topiramate and zonisamide are associated with numerous clinically significant interactions.

Finally, in the past few years, interactions relating to the selective inhibition of the metabolism of carbamazepine to its epoxide metabolite, or subsequent metabolism of the epoxide, have been described. These may have considerable clinical significance, particularly since there is increasing evidence to suggest that the epoxide may contribute not only to the efficacy of carbamazepine but also to its toxicity. Carbamazepine epoxide plasma concentrations can be quadrupled in some patients by valproate, usually in the absence of changes in carbamazepine, and precipitating toxicity. With the more widespread availability of therapeutic monitoring of the epoxide, these interactions are increasingly being identified.

Further reading

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CHAPTER 32

Stopping antiepileptic drug treatment

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Around 60 to 70% of people on antiepileptic drug (AED) treatment will eventually become seizure free. One may consider drug withdrawal after 'remission'; a period of seizure freedom, generally in adult practice 3-5 years is sensible, though is typically shorter in paediatrics. This is often at the patients request due to concerns about long term side effects and need to take daily medications. Key factors to consider when withdrawing AEDs is the type and severity of the epilepsy. It is not known, however, whether this remission represents sustained change in seizure threshold in that person's epilepsy or whether 'control' is dependent on continued AED therapy. Currently there is no ideal test to determine risk of future seizures when drugs are withdrawn. Previous investigations with MRI or EEG that determine the cause of epilepsy and/or syndrome of course can help give an indication of future seizure recurrence without medication.

The probability of relapse after stopping treatment has varied between 11-41% in different studies. The final decision to come off treatment should be taken in partnership between the individual and their physician. Since the safety of drug withdrawal cannot be guaranteed in any one case, this means asking people to judge the relative risks of continued drug taking against the risk of further seizures inherent in drug withdrawal. This decision becomes more difficult as people with epilepsy pass from their school years into full adult life, where driving and employment may be impacted by seizure recurrence. Children and adolescents seen by paediatricians are more likely to come off medication after a period of remission than those seen by an adult neurologist - this is because of good remission in some paediatric epilepsies, changes in seizure thresholds as the brain matures and adverse effects of AEDs on cognition. If a decision to withdraw medication is made, discontinuation of treatment should be undertaken slowly, possibly over a period of months, to minimise the risks of relapse¹.

Medical factors

The risk of relapse for children in remission is about 20% overall. Whereas in series which included adults, relapse rates are approximately 40%^{1,2}. Of course, even with uninterrupted treatment there is also a risk of relapse. For instance, in one large study, people in long-term remission were randomised either to continue or withdraw treatment; the risk of relapse in the first two years after randomisation was 41% in those coming off treatment and 22% in those continuing on medication³. A higher risk of recurrence is correlated with both the prior use of multiple AEDs and generalised tonic-clonic seizure types³. Most relapses occur within the first year of treatment reduction or withdrawal. Factors associated with increased risk of seizure recurrence include an abnormal neurologic examination, IQ less than 70, longer duration of epilepsy, higher number of seizures, multiple seizure types, focal epileptiform abnormalities on EEG, longer duration of disease and earlier age of onset prior to the period of seizure freedom⁴. Juvenile myoclonic epilepsy (JME) or the presence of a brain structural lesion underlying the epilepsy also enhances the risk of relapse.

Whether EEG is helpful is controversial. Certainly only those EEGs taken after a period of remission are likely to be of value. In children, there seems little doubt that the presence of persisting EEG abnormalities has an adverse prognostic influence but whether this is true in adults remains uncertain.

People must set the risks of drug withdrawal against those of continued therapy and these are difficult to quantify. Social complications of failed drug withdrawal increase with adulthood and trials of drug withdrawal should ideally take place before school-leaving age. After this a number of factors may influence decision making.

Employment

The young person with a history of epilepsy is more likely to find difficulty gaining satisfactory employment. Continued remission of epilepsy greatly enhances the chance of employment and this usually acts as a pressure to continue therapy. On rare occasions, however, the contrary may be true. Some employers may make an offer of employment conditional on an individual being off medications.

Driving

At 17 a young person with a history of epilepsy can gain a provisional driving licence in the UK as long as he/she has either been free of seizures altogether for a period of one year, or has only suffered nocturnal seizures for a period of three years. The possession of a driving licence is a potent deterrent for the discontinuation of therapy, as any seizure occurring on drug withdrawal will inevitably lead to its loss and this may secondarily affect employment. The current UK DVLA regulations (2017)⁵, are a recommendation that driving should cease during the period of medicine withdrawal, and for 6 months after withdrawal is complete. The DVLA does not need to be informed unless a seizure were to occur. If a seizure occurs during drug withdrawal, patients need to inform the DVLA and surrender their licence. Generally people with epilepsy need to be seizure free for 12 months for re-licencing. A recent change in the regulations is that the licence may be regained sooner than 12 months if the following is satisfied 1) the patient was controlled prior to AED reduction, 2) the seizure occurred as a result of a documented clinician directed reduction in AED, 3) treatment has been reinstated for at least 6 months and the patient is seizure free whilst back on treatment. In case of doubt enquiries and advice need to be sought from the DVLA.

Leisure pursuits

A person with epilepsy often enjoys participation in activities that might be viewed as 'unsafe' if a seizure were to occur. These include swimming, cycling, being at heights and horse riding, all of which can be undertaken satisfactorily with a few common-sense precautions and responsible supervision. Such pursuits may, however, be regarded as unacceptably risky during a period of AED discontinuation, and generally applying the same advice as that required by the DVLA for licencing is appropriate.

Contraception and pregnancy

Concern about the effect of AEDs on contraception and pregnancy is very real to young women with epilepsy (see Chapter 45). The fact that some AEDs (phenobarbitone, phenytoin, carbamazepine and topiramate) may reduce the efficacy of oral contraceptive agents and necessitate the use of higher-dose oestrogen preparations may be seen by many as an indication for considering AED withdrawal. A more potent argument, however, is the risk of teratogenicity associated with drug therapy. Most young women contemplating pregnancy who have been seizure free for

approximately 2–3 years would see this as a reason for considering a trial of AED withdrawal before pregnancy. However, again this needs to be an individualised decision, influenced by the type of epilepsy, with higher rates of seizure recurrence in the idiopathic generalised epilepsies.

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CHAPTER 33

Treatment of tonic-clonic status epilepticus**MATTHEW C. WALKER**

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Tonic-clonic status epilepticus was defined as a condition in which prolonged or recurrent tonic-clonic seizures persist for 30 minutes or more. However, although this definition has been successfully applied to epidemiological studies, it lacked a practical perspective. So status epilepticus is now defined as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury and alteration of neuronal networks, depending on the type and duration of seizures. For tonic-clonic status epilepticus, $t_1 = 5$ minutes and $t_2 = 30$ minutes.

The annual incidence of tonic-clonic status epilepticus has been estimated to be approximately 18–28 cases per 100,000 persons (9000–14,000 new cases each year in the United Kingdom, or 45,000–70,000 cases in the United States), and these estimates have been largely confirmed in population-based studies. Tonic-clonic status epilepticus is most frequent in children, the mentally handicapped and in those with structural cerebral pathology (especially in the frontal areas). In established epilepsy, status epilepticus can be precipitated by drug withdrawal, intercurrent illness or metabolic disturbance, or the progression of the underlying disease, and is commoner in symptomatic than in idiopathic epilepsy. About 5% of all adult clinic patients with epilepsy will have at least one episode of status epilepticus in the course of their epilepsy, and in children the proportion is higher (10–25%). Status epilepticus accounts for about 3.5% of admissions to neurological intensive care, and 0.13% of all visits to a university hospital casualty department. The mortality of status epilepticus is about 20%, most patients dying of the underlying condition rather than the status epilepticus itself or its treatment, and reassuringly the mortality seems to be decreasing in the last 20 years possibly due to improved management of acute seizures and status epilepticus. Permanent neurological and mental deterioration may result from status epilepticus, particularly in young children; the risks of morbidity are greatly increased the longer the duration of the status epilepticus episode.

General measures

For the new patient presenting as an emergency in status epilepticus, it is helpful to plan therapy in a series of progressive phases (see Table 1).

1st stage (0–10 minutes)

Oxygen and cardiorespiratory resuscitation. It is first essential to assess cardiorespiratory function, to secure the airway, and to resuscitate where necessary. Oxygen should always be administered, as hypoxia is often severe.

Table 1. General measures for the patient presenting with tonic-clonic status epilepticus.

1st stage (0-10 minutes)

- Assess cardiorespiratory function
- Secure airway and resuscitate
- Administer oxygen

2nd stage (0-60 minutes)

- Institute regular monitoring (see text)
- Emergency AED therapy (see text)
- Set up intravenous lines
- Emergency investigations (see text)
- Administer glucose (50 ml of 50% solution) and/or intravenous thiamine (250 mg) as high potency intravenous Pabrinex where appropriate
- Treat acidosis if severe

3rd stage (0-60/90 minutes)

- Establish aetiology
- Identify and treat medical complications
- Pressor therapy when appropriate

4th stage (30-90 minutes)

- Transfer to intensive care
- Establish intensive care and EEG monitoring (see text)
- Initiate intracranial pressure monitoring where appropriate
- Initiate long-term, maintenance, antiepileptic therapy

These four stages should be followed chronologically; the 1st and 2nd within 10 minutes, and stage 4 (transfer to intensive care unit) in most settings within 60-90 minutes of presentation.

2nd stage (0-60 minutes)

Monitoring. Regular neurological observations and measurements of pulse, blood pressure, ECG and temperature should be initiated. Metabolic abnormalities may cause status epilepticus, or develop during its course, and biochemical, blood gas, pH, clotting, and haematological measures should be monitored.

Emergency anticonvulsant therapy should be started.

Intravenous lines should be set up for fluid replacement and drug administration (preferably with 0.9% sodium chloride (normal or physiological saline) rather than 5% glucose solutions). Drugs should not be mixed and, if two antiepileptic drugs (AEDs) are needed (for example, phenytoin and diazepam), two intravenous lines should be sited. The lines should be in large veins, as many AEDs cause phlebitis and thrombosis at the site of infusion. Arterial lines must never be used for drug administration.

Emergency investigations. Blood should be drawn for the emergency measurement of blood gases, sugar, renal and liver function, calcium and magnesium levels, full haematological screen (including platelets), blood clotting measures and anticonvulsant levels; 50 ml of serum should also be saved for future analysis especially if the cause of the status epilepticus is uncertain. Other investigations depend on the clinical circumstances.

Intravenous glucose and thiamine. If hypoglycaemia is suspected, 50 ml of a 50% glucose solution should be given immediately by intravenous injection. If there is a history of alcoholism, or other compromised nutritional states, 250 mg of thiamine (for example, as the high potency intravenous formulation of Pabrinex, 10 ml of which contains 250 mg) should also be given intravenously. This is particularly important if glucose has been administered, as a glucose infusion increases the risk of Wernicke's encephalopathy in susceptible patients. Intravenous high-dose thiamine should be given slowly (for example, 10 ml of high potency Pabrinex over 10 minutes), with facilities for treating anaphylaxis. Routine glucose administration in non-hypoglycaemic patients should be avoided as there is some evidence that this can aggravate neuronal damage.

Acidosis. If acidosis is severe, the administration of bicarbonate has been advocated in the hope of preventing shock and mitigating the effects of hypotension and low cerebral bloodflow. In most cases, however, this is unnecessary and more effective is the rapid control of respiration and abolition of motor seizure activity.

3rd stage (0-60/90 minutes)

Establish aetiology. The range of causes of status epilepticus depends primarily on age and the presence or absence of established epilepsy. The investigations required depend on clinical circumstances; CT or MRI and CSF examination are often required. The latter should be carried out only with facilities for resuscitation available as intracranial pressure is often elevated in status epilepticus. If the status epilepticus has been precipitated by drug withdrawal, the immediate restitution of the withdrawn drug will usually rapidly terminate the status epilepticus.

Physiological changes and medical complications. The physiological changes of uncompensated status epilepticus may require specific therapy. Active treatment is most commonly required for: hypoxia, hypotension, raised intracranial pressure, pulmonary oedema and hypertension, cardiac arrhythmias, cardiac failure, lactic acidosis, hyperpyrexia, hypoglycaemia, electrolyte disturbance, acute hepatic or renal failure, rhabdomyolysis, or disseminated intravascular coagulation.

Pressor therapy. Failure to correct hypotension can lead to significant cerebral ischaemia and so blood pressure should be maintained by correcting hypovolaemia and if necessary through the use of pressor agents such as adrenaline, noradrenaline and dobutamine. These agents are almost invariably required in patients sedated with barbiturate anaesthesia.

4th stage (30-90 minutes)

Intensive care. If seizures are continuing in spite of the measures taken above, the patient must be transferred to an intensive care environment.

Intensive care monitoring. In severe established status epilepticus, intensive monitoring may be required, including: intra-arterial blood pressure, capnography, oximetry, central venous and pulmonary artery pressure monitoring.

Magnesium. Although effective in preventing eclampsia, there is no evidence to suggest that increasing magnesium serum concentrations to supranormal levels has any benefit in status epilepticus. Indeed, such a policy can result in motor paralysis, difficulty in detecting clinical seizure activity and hypotension. However, serum magnesium can be low in alcoholics and patients on medication for HIV, and in these patients intravenous loading with 2-4 g of magnesium sulphate over 20 minutes may help with seizure control and prevention of arrhythmias.

Seizure and EEG monitoring. In prolonged status epilepticus, or in comatose ventilated patients, motor activity can be barely visible. In this situation, continuous EEG monitoring using a full EEG or a cerebral function monitor is necessary, and at the very least intermittent daily EEGs should be recorded. The latter must be calibrated individually to register both burst-suppression and seizure activity. Burst-suppression provides an arbitrary physiological target for the titration of barbiturate or anaesthetic therapy. Drug dosing is commonly set at a level that will produce burst-suppression with interburst intervals of between 2 and 30 seconds.

Intracranial pressure monitoring and cerebral oedema. Continuous intracranial pressure monitoring is sometimes needed, especially in children in the presence of persisting, severe, or progressive elevated intracranial pressure. The need for active therapy is usually determined by the underlying cause rather than the status epilepticus. Intermittent positive pressure ventilation, high-dose corticosteroid therapy (4 mg dexamethasone every six hours), or mannitol infusion may be used (the latter is usually reserved for temporary respite for patients in danger of tentorial coning). Neurosurgical decompression is occasionally required.

Long-term anticonvulsant therapy. Long-term, maintenance, anticonvulsant therapy must be given in tandem with emergency treatment. The choice of drug depends on previous therapy, the type of epilepsy, and the clinical setting. If phenytoin or phenobarbitone has been used in emergency treatment, maintenance doses can be continued orally (through a nasogastric tube) guided by serum level monitoring. Other maintenance AEDs can be started also, giving oral loading doses. Care needs to be taken with nasogastric feeds, which can interfere with the absorption of some AEDs (especially phenytoin).

Treatment of tonic-clonic status epilepticus

Tonic-clonic status epilepticus is treated as an emergency in order to avoid both systemic complications and also cerebral damage. Cerebral damage is partly caused by physiological compromise and the consequent hypoxia/ischaemia, but it also results from excitotoxicity consequent upon continuous seizure activity. In the initial stages of a tonic-clonic seizure, there are compensatory mechanisms that result in increased cerebral perfusion. By 60–90 minutes these compensatory mechanisms fail; there is hypotension and, importantly, loss of cerebral autoregulation. This results in cerebral hypoperfusion and cerebral damage. In addition, at this stage, the continuous seizure activity results in intraneuronal calcium accumulation and neuronal death. Thus, treatment regimens should be staged. These stages are: the premonitory (pre-hospital) stage, the early status epilepticus stage from 0–30 minutes, the stage of established status epilepticus from 30–60/90 minutes and then the refractory (late) stage during which substantial neuronal damage can occur.

Stages in emergency drug treatment

The suggested regimen for a typical new case presenting to a casualty department as an emergency is given in Table 2. These are guidelines, and obviously in some circumstances intensive care management and general anaesthesia may be required earlier.

Premonitory stage

In patients with established epilepsy, tonic-clonic status epilepticus seldom develops without warning. Usually, a prodromal phase (the premonitory stage), during which seizures become increasingly frequent or severe, precedes status epilepticus. Urgent drug treatment will usually prevent the evolution into true status epilepticus. If regular AED treatment has been reduced or stopped by patient or doctor, this should be reinstated. Rectal diazepam was the drug of choice. A dose of 0.5–1 mg/kg rectal diazepam solution results in therapeutic serum concentrations

within one hour, and has been shown to be very effective in arresting acute seizures with minimal side effects.

However, a disadvantage of rectal diazepam is difficulty with and concern about the route of administration, especially in children so alternatives have been sought. Midazolam has the advantage over other benzodiazepines in that it can be administered by intranasal, buccal and intramuscular routes. Buccal midazolam (10 mg in 2 ml) has shown superiority over rectal diazepam in trials in children, and is now the drug of choice in children and adults. Recent evidence has indicated that intramuscular midazolam is a superior treatment to intravenous lorazepam when given by paramedics prior to hospitalisation due to improved speed of administration and should certainly be considered in all instances in which intravenous access is difficult.

Table 2. Suggested emergency antiepileptic drug regimen for status in newly presenting adult patients.

Premonitory stage (pre-hospital)	Midazolam 10 mg given buccally <i>If seizures continue, treat as below</i>
Early status	Lorazepam (4 mg i.v.) repeated once after 10 minutes. If intravenous access is not easily achieved then midazolam (10 mg i.m.) should be considered. <i>If seizures continue 30 minutes after first injection, treat as below</i>
Established status	Phenytoin infusion at a dose of 20 mg/kg at a rate of 50 mg/minute or fosphenytoin infusion at a dose of 20 mg PE/kg at a rate of 150 mg PE/minute or Valproate infusion at a dose of 40 mg/kg (maximum dose 300 mg over 10 minutes) or Levetiracetam infusion at a dose of 60 mg/kg (maximum dose 4500 mg) over 10 minutes
Refractory status	General anaesthesia, with either propofol, midazolam or thiopentone. Anaesthetic continued for 12–24 hours after the last clinical or electrographic seizure, then dose tapered

In the above scheme, the refractory stage (general anaesthesia) is reached 60/90 minutes after the initial therapy. This scheme is suitable for usual clinical hospital settings. In some situations, general anaesthesia should be initiated earlier and, occasionally, should be delayed.

The earlier treatment is given the better. It is easier to prevent the evolution of epilepsy to status epilepticus than to treat the established condition. If the patient is at home, AEDs should be administered before transfer to hospital or in the casualty department before transfer to the ward. The acute administration of either diazepam or midazolam will cause drowsiness or sleep, and rarely cardiorespiratory collapse, and patients should be carefully supervised.

Early status epilepticus (0–30 minutes)

Once status epilepticus has developed, treatment should be carried out in hospital, under close supervision. For the first 30–60 minutes or so of continuous seizures, physiological mechanisms compensate for the greatly enhanced metabolic activity. This is the stage of *early status epilepticus* and it is usual to administer a fast-acting benzodiazepine.

In most clinical settings, intravenous *lorazepam* (0.07 mg/kg to a maximum of 4 mg) is the drug of choice, and this dose can be repeated once if seizure activity does not stop. Other benzodiazepines such as diazepam, clonazepam and midazolam are alternatives but, due to its more prolonged action, lorazepam should be preferred. If intravenous access is not easily available then intramuscular midazolam 10mg is an alternative. In most patients, therapy will be highly effective. Continuous 24-hour inpatient observation should follow. In previously non-epileptic patients, long-term AED therapy should be considered, and in those already on maintenance antiepileptic therapy, this should be reviewed.

Established status epilepticus (30–60/90 minutes)

At this stage physiological decompensation will usually have begun. Intensive care facilities are desirable. There are four alternative treatment options. These are phenytoin (20 mg/kg), fosphenytoin (a phenytoin pro-drug), valproate (40 mg/kg) and levetiracetam (60mg/kg); all are given by intravenous loading followed by repeated oral or intravenous supplementation. Valproate should be avoided in those with a urea cycle deficit, liver disease or mitochondrial disease. There is, at present, an on-going blinded randomised control trial to determine which of these should be the preferred option.

Refractory status epilepticus (after 60/90 minutes)

If seizures continue for 60–90 minutes after the initiation of therapy, the stage of refractory status epilepticus is reached and full anaesthesia required. In many emergency situations (for example, post-operative status epilepticus, severe or complicated convulsive status epilepticus, patients already in intensive care), anaesthesia can and should be introduced earlier. Prognosis will now be much poorer, and there is a very high mortality and morbidity.

Anaesthesia can be induced by barbiturate or non-barbiturate drugs. A number of anaesthetics have been administered, although few have been subjected to formal evaluation and all have drawbacks. The most commonly used anaesthetics are the intravenous barbiturate *thiopentone*, the intravenous non-barbiturate *propofol* or continuous *midazolam* infusion. A non-randomised comparison of propofol and thiopentone was unable to detect any clinically significant differences between the drugs. Other drugs in current use include the intravenous anaesthetic pentobarbitone (not available in the UK).

At this stage, the use of immunosuppression with steroids and even intravenous immunoglobulin/plasma exchange should be considered, as there is growing evidence for the role of autoantibodies (especially against NMDA receptors) in the aetiology of refractory status epilepticus.

Patients require the full range of intensive care facilities, including EEG monitoring, and care should be shared between anaesthetist and neurologist. Experience with long-term administration (hours or days) of the newer anaesthetic drugs is very limited. The modern anaesthetics have, however, important pharmacokinetic advantages over the more traditional barbiturates.

Once the patient has been free of seizures for 12–24 hours and provided that there are adequate plasma levels of concomitant antiepileptic medication, then the anaesthetic should be slowly tapered.

Further reading

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CHAPTER 34

Treatment of non-convulsive status epilepticus**MATTHEW C. WALKER**

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Introduction

Seizures of any type can continue unabated and they are then considered as a separate entity, status epilepticus. This is of great importance, as in certain circumstances a persistent seizure can result in neuronal damage irrespective of any physiological compromise.

Among the diagnoses of status epilepticus are a number that can be considered as non-convulsive status epilepticus including absence status epilepticus, atypical absence status epilepticus, electrical status epilepticus during slow-wave sleep (including Landau-Kleffner syndrome), complex partial status epilepticus and status epilepticus in coma. Indirect estimates for the incidence of non-convulsive status epilepticus have been as high as 14–24 per 100,000 population per year (the majority of these are non-convulsive status epilepticus in the setting of learning difficulties). Although non-convulsive status epilepticus includes a number of very different conditions, these forms of status epilepticus share two important qualities: difficulty in making the diagnosis and uncertainty about the best mode of treatment.

Diagnosis

The diagnosis of non-convulsive status epilepticus can be difficult, and is dependent on EEG. In patients with a previous diagnosis of epilepsy, any prolonged change in personality, prolonged post-ictal confusion (greater than 20 minutes) or recent onset psychosis should be investigated with EEG as these can all be presentations of non-convulsive status epilepticus. If new onset developmental delay occurs in the setting of epilepsy then a sleep EEG should be considered to look for status epilepticus during slow-wave sleep (see below). In non-comatose patients with no history of epilepsy, non-convulsive status epilepticus can present as confusion or personality change (almost invariably in the setting of a metabolic derangement, encephalitis or other acute precipitant). Rarely, non-convulsive status epilepticus can present as autism and if suspicions are raised (usually a fluctuating course) then EEG is indicated.

Non-convulsive status epilepticus can follow convulsive status epilepticus, and is an important treatable cause of persistent coma following convulsive status epilepticus. This and status epilepticus with subtle manifestations such as twitching of the limbs, or facial muscles or nystagmoid eye jerking, which can result from hypoxic brain damage, are often collectively referred to as subtle motor status epilepticus. Up to 8% of patients in coma who have no outward signs of seizure activity are in non-convulsive status epilepticus thus emphasising the importance of EEG in the investigation of comatose patients. Similarly, non-convulsive status epilepticus is underdiagnosed in the confused elderly in whom the confusion is frequently blamed on other causes.

Although EEG interpretation is usually straightforward, with regular repetitive discharges occurring in some patients in a cyclical fashion, difficulties can occur in differentiating non-convulsive status epilepticus from an encephalopathy of other cause. Thus electrographic definitions of non-convulsive status epilepticus should include: unequivocal electrographic seizure activity; periodic epileptiform discharges or rhythmic discharge with clinical seizure activity; and rhythmic discharge with either clinical or electrographic response to treatment. There is uncertainty about the relevance of periodic lateralised epileptiform discharges (PLEDs). This is most notable following severe encephalitis or hypoxic injury in which discharges can occur with such periodicity so as to be confused with periodic discharges seen following prolonged status epilepticus. Some have argued that such discharges represent ongoing seizure activity, and should be treated thus. The general consensus, however, is that a multitude of aetiologies can underlie PLEDs and that they should only be treated as epileptic if there is other evidence of ictal activity.

Neuronal damage and non-convulsive status epilepticus

It has long been recognised that ongoing electrographic seizure activity can result in neuronal damage, so-called excitotoxic neuronal damage. This damage occurs in animal models of non-convulsive status epilepticus. These animal models, however, involve the induction of status epilepticus in non-epileptic animals with either powerful chemoconvulsants or prolonged high frequency repetitive stimulation. This is very different from the human situation. Furthermore, non-convulsive status epilepticus in humans tends to have lower frequency discharges, which if reproduced in animal models produces substantially less neuronal damage.

Another important finding has been that epileptic animals, animals pretreated with antiepileptic drugs (AEDs) and young animals are all resistant to chemoconvulsant induced neuronal damage. Thus young age, AEDs and prior history of epilepsy probably all confer some degree of neuroprotection. Lastly, in humans, non-convulsive status epilepticus often results from an acute precipitant such as an encephalitis and, in such circumstances, the status epilepticus only minimally contributes to any resultant pathology.

There have been reports of prolonged memory problems, hemiparesis and death occurring following complex partial status epilepticus although, in most of these cases, the outcome relates to the underlying aetiology. Indeed, the degree to which non-convulsive status epilepticus contributes to neuronal damage in humans is unclear. Since aggressive treatment is not entirely benign, and can lead to hypotension and respiratory arrest, then the best approach to treatment will only be determined in randomised studies of aggressive versus more conservative management.

Specific forms of non-convulsive status epilepticus

Typical absence status epilepticus

This entity needs to be distinguished from complex partial status epilepticus and atypical absences seen in mental retardation. This term should perhaps be reserved for prolonged absence attacks with continuous or discontinuous 3 Hz spike and wave occurring in patients with primary generalised epilepsy. The EEG, however, may also include irregular spike and wave, prolonged bursts of spike activity, sharp wave or polyspike and wave.

Although absence epilepsy has its peak in childhood and commonly remits in adolescence, absence status epilepticus commonly occurs in later life. Absence status epilepticus can be divided into childhood absence status epilepticus (those usually already receiving treatment), late-onset absence status epilepticus with a history of primary generalised seizure (often a history of absences in childhood) and late-onset absence status epilepticus developing *de novo* (usually following drug or alcohol withdrawal).

There is no evidence that absence status induces neuronal damage, and thus aggressive treatment is not warranted. Treatment can either be intravenous or oral. Absence status epilepticus is often precipitated by the prescription of inappropriate AEDs in idiopathic generalised epilepsy (e.g. carbamazepine). Absence status epilepticus responds rapidly to intravenous benzodiazepines, and these are so effective that the response is diagnostic. Lorazepam at 0.05–0.1 mg/kg is the benzodiazepine of choice. The effect may only be transient and a longer acting AED may need to be given. If intravenous treatment is required but either benzodiazepines are ineffective or contraindicated then intravenous valproate (20–40 mg/kg) can be given. In cases of primary generalised epilepsy, treatment should be continued with a suitable AED. If a precipitating factor can be identified in late-onset *de novo* cases, then long-term therapy is not usually indicated.

Complex partial status epilepticus

Complex partial status epilepticus has to be differentiated not only from other forms of non-convulsive status epilepticus, but also from post-ictal states, and other neurological and psychiatric conditions. EEG can be helpful but often the scalp EEG changes are non-specific and the diagnosis is very much clinical in nature. The definition as ‘a prolonged epileptic episode in which focal fluctuating or frequently recurring electrographic epileptic discharges, arising in temporal or extratemporal regions, result in a confusional state with variable clinical symptoms’ is suitably vague and is necessary to emphasise that complex partial status epilepticus can originate in any cortical region and can fluctuate in a cyclical fashion. A further factor is importantly included in this definition, and that is the absence of coma; electrographic status epilepticus in coma is considered separately, partly because of its poor prognosis.

How aggressively complex partial status epilepticus should be treated depends upon: the prognosis of the condition and whether treatment improves the prognosis. As in all epilepsies the prognosis relates partly to the prognosis of the underlying aetiology and any concomitant medical conditions. Complex partial status epilepticus in someone with epilepsy is probably a more benign condition than acute precipitated status epilepticus, and should perhaps be treated thus. The medication used to treat status epilepticus is not without adverse effects and can result in hypotension, respiratory depression and, sometimes, cardio-respiratory arrest. This is more so with intravenous administration with its resultant rapid, high serum levels. At present, early recognition of the condition and treatment with oral or rectal benzodiazepines is recommended; oral clobazam has proven to be an effective treatment. In patients who have repetitive attacks of complex partial status epilepticus, oral clobazam (10–20 mg/day) over a period of 2–3 days given early at home can usually abort the status epilepticus, and such strategies should be discussed with patient and carers.

Early recognition is a critical goal, as the delay in treatment comes not from therapeutic strategy but from failure to diagnose the condition in the first place. For more persistent or resistant complex partial status epilepticus, intravenous therapy should be used, and lorazepam followed by phenytoin are the drugs of choice. In contrast to absence status epilepticus, the response to benzodiazepines can be disappointing and often there is a resolution of the electrographic status epilepticus without concomitant clinical improvement (possibly due to post-ictal effects). Whether general anaesthesia is ever justified remains a matter for speculation; since most complex partial status epilepticus is self-terminating often without any serious neurological sequelae, then such aggressive therapy should, in most instances, be avoided. Treatment of the underlying cause (e.g. encephalitis or metabolic derangement) is of course paramount and can often lead to resolution of the status epilepticus.

Atypical absence status epilepticus

Atypical absence status epilepticus is associated with the epileptic encephalopathies such as Lennox-Gastaut syndrome. This entity can be difficult to diagnose, but should be considered

if there is change in personality, decrease in cognition or increased confusion in a patient with one of these epilepsies. The EEG characteristics are usually that of continuous or frequent slow (< 2.5 Hz) spike and wave. This condition is usually poorly responsive to intravenous benzodiazepines, which should, in any case, be given cautiously, as they can induce tonic status epilepticus in these patients. Oral rather than intravenous treatment is usually more appropriate, and the drugs of choice are valproate, lamotrigine, topiramate, clonazepam and clobazam. Sedating medication, carbamazepine and vigabatrin have been reported to worsen atypical absences.

Non-convulsive status epilepticus in coma

Electrographic status epilepticus in coma is not uncommon and is seen in up to 8% of patients in coma with no clinical evidence of seizure activity. The diagnosis is often debatable as in many instances burst-suppression patterns, periodic discharges and encephalopathic triphasic patterns have been proposed to represent electrographic status epilepticus, while these mostly indicate underlying widespread cortical damage or dysfunction. Non-convulsive status epilepticus in coma consists of three groups: those who had convulsive status epilepticus, those who have subtle clinical signs of seizure activity and those with no clinical signs. Convulsive status epilepticus has, as part of its evolution, subtle status epilepticus in which there is minimal or no motor activity but ongoing electrical activity. This condition should be treated aggressively with deep anaesthesia and concomitant AEDs. The association of electrographic status epilepticus with subtle motor activity often follows hypoxic brain activity and has a poor prognosis, but aggressive therapy with benzodiazepines, phenytoin and increased anaesthesia is perhaps justified, since the little evidence available indicates that such treatment improves prognosis.

Lastly electrographic status epilepticus with no overt clinical signs is difficult to interpret - does it represent status epilepticus or widespread cortical damage? Since these patients have a poor prognosis, aggressive treatment is recommended in the hope that it may improve outcome. Lastly there is a group of patients in whom there are clinical signs of repetitive movements, but no electrographic seizure activity, and in these patients antiepileptic treatment and aggressive sedation is not recommended.

Conclusion

Non-convulsive status epilepticus is an all-encompassing term that covers a variety of conditions with very different prognoses, from the entirely benign to the fatal (although this is mainly due to the underlying aetiology). These conditions are poorly replicated by available animal models, and this together with the lack of randomised treatment trials has meant that the best treatment options are unknown. It is important to remember that aggressive AED treatment is not benign especially when deep anaesthesia is proposed.

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CHAPTER 35

Non-pharmacological treatments for epilepsy

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Introduction

The use of 'alternative', 'complementary' and 'conventional' as adjunctive terms in medicine has emerged from a predominantly Western perspective on the treatment of disease. Definitions of what constitutes a complementary or alternative medicine (CAM) vary, but CAM is generally used as an umbrella term to refer to any treatment that falls outside the sphere of the conventional Western medical school syllabus. While many CAM treatments are derived from mystical or spiritual schemas of understanding of health and disease, others are based on theories and hypotheses that depart from mainstream scientific thinking.

Some have suggested that the alternative versus conventional distinction for medical treatments is irrelevant, since the only important distinction in medicine is whether something works or not. If it works, it's a treatment, if it doesn't, it's not. This approach has considerable clinical appeal. Any treatment approach in epilepsy that is effective in controlling seizures should be given serious consideration. Although antiepileptic medications have proven efficacy, they are not universally effective. Up to one-third of patients continue to experience seizures even when they are taking multiple antiepileptic drugs (AEDs). Even if conventional AED's are effective in controlling seizures, some people may look to CAM as they are not able to tolerate the side effects that accompany these medications. People with epilepsy will often consult their neurologist about the advisability of adding CAM therapies to their treatment regimen. While neurologists are not expected to be experts in every CAM approach, they should have some awareness of the dangers, interactions and possible benefits of these treatments for their patients.

The evidence base and rationale behind some of the most popular CAM approaches in epilepsy are briefly summarised in Table 1. However, with the multitude of CAM therapies available today, it is beyond the scope of this short chapter to review every one. For a more comprehensive evaluation of each treatment, readers are directed towards *'Epilepsy: Comprehensive and Alternative Treatments'*. This is also a useful, accessible resource to point patients towards, if they are interested in pursuing CAM treatments for their epilepsy.

Standards of evidence

The gold standard test of any treatment in conventional Western medicine is a randomised controlled trial (RCT), double-blind, with a crossover design. With the exception of traditional Chinese medicine (TCM), very few CAM therapies have been subjected to this scientific rigour. Although some CAM therapists assert that scientific evaluation is antithetical to their treatment philosophy, the limited evidence base for most alternative treatments is frequently due to a lack of research funding and inadequate practitioner training in evidence-based medicine. With the right methodology it should be possible to prove the efficacy of any treatment. It is relatively

straightforward to find out whether something works or not, regardless of its provenance. In the absence of any well conducted trials, the evidence base for many CAM approaches has to be limited to an evaluation of the ideas and philosophy that underpin the approach, backed up with occasional, poorly controlled, case reports. Case-controlled designs and cohort studies are relatively rare, but those that have been reported can provide useful data to direct future research towards the most promising approaches.

Holistic approaches

Many CAM treatments are based on a holistic approach to wellness. Practitioners often offer bespoke treatment programmes, taking account of the person and their social and physical environment. This is in marked contrast to Western medicine where most people will go through a standardised procedure, initially trying one of the ‘first line’ drugs at a standard dose when they are first diagnosed with epilepsy. In Western medicine, individualised treatment plans evolve over time if the first line medications do not work and more drugs need to be added and withdrawn to achieve control. The whole-person approach is often missing in conventional medicine, where the disease or symptoms are the primary focus of the physician, rather than the person. This is evidenced by the elaborate classification systems and schema for symptoms and presentations, with no reference to the person experiencing them. Regardless of the ideas or philosophies that underlie the various holistic approaches in CAM, it is possible that the holistic approach, in and of itself, may confer tangible, clinical benefits in epilepsy, via indirect effects on anxiety, depression and other aspects of psychological wellbeing.

The power of the placebo

The placebo effect is a real phenomenon that produces tangible, replicable results in a wide variety of patients, including those with epilepsy. The literature is clear; patients receiving placebos do better than those who receive no treatment at all.

Holistic approaches tend to tick all the boxes when it comes to the attributes a placebo needs to maximise its effectiveness. The remedy is prescribed by a practitioner who has a firm belief that it works. They often conduct a very thorough, deeply personal interview with the patient, asking them about almost every aspect of their lives including events, sensations, memories, dreams, emotions and thoughts. This deep interest in the patient is an integral part of creating the remedy. The rituals surrounding the preparation of the remedies are frequently elaborate, shrouded in metaphysical concepts, or ancient wisdom, and the result is a bespoke treatment. If someone were to pull together all the scientific data on the placebo effect and create the optimal approach, it would look very like many of the popular holistic treatment approaches available today.

This is clearly illustrated in Queen Square, London. Queen Square is home to the Hospital for Integrative Medicine (formerly the Royal Homeopathic Hospital). The hospital is a smart clean, cream building with a light and spacious, modern interior. A patient attending this hospital will be the absolute centre of care and attention while a homeopathic practitioner takes a more detailed history than they will have ever experienced in a traditional neurology clinic or in the six minutes normally allotted to them at their NHS GP surgery. After a long face-to-face consultation, they will leave with a medicine specifically chosen and designed not just for their symptoms but their wider circumstances too.

The Hospital for Integrative Medicine is next door to and indeed shares a party wall with the Department of Clinical and Experimental Epilepsy at the National Hospital for Neurology and Neurosurgery. The National Hospital is an old Victorian hospital of dull red brick. On entering the patient is immediately confronted by the NHS green walls and scuffed floor as they head for

the crowded, windowless, outpatient waiting room, where they will wait, (sometimes for hours) to see a junior doctor they may have never met before, who may (or may not) have had time to read their notes and who will be under immense pressure to get them out of the door as soon as possible in order to see the next patient and stop the clinic over-running even longer. The doctor may prescribe a new medication but will be at pains to point out that the chances of it working at this point in their condition may be 10% or less. This may be a worst case scenario, but you can guess which of these patients would probably feel better about their condition and more in control as they leave their respective hospitals and make their way home across the square.

There is often little or no empirical evidence to support many of the complementary and alternative therapies for epilepsy. However an absence of evidence is not the same as evidence of absence and some CAM therapies can play an important role in the treatment of epilepsy. Western and holistic medical traditions can learn from each other and there is much in the CAM world that should stimulate the interest and research expertise of epileptologists looking to broaden the range of effective options they can offer their patients, beyond the realm of antiepileptic medications. As Dr John Hughes-Games, a GP, and the former president of the faculty of homeopathy at the Bristol Homeopathic Hospital said...

‘The best way to recover from an illness would be to have someone or something evoke (a) healing response – no drugs, no knives – splendid! Indeed if homeopathy were only a superb way of producing a placebo response, its existence would be more than justified by that alone.’

Psychological Approaches in Epilepsy

A recent Cochrane review of the evidence for psychological interventions in people with epilepsy noted the poor quality of many studies in this field with high levels of attrition in studies that required active participant participation. However some psychological interventions that target training in the self-management of seizures are associated with improvements in quality of life and emotional well-being in this population. These approaches can also be useful in helping people with epilepsy reduce the fatigue that can be associated with seizures and the side effects of treatment. Unfortunately, psychologists with the expertise to provide such treatment are few and far between and this is not a treatment available to the majority of people with epilepsy.

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Table 1. Brief overview of the rationales and evidence base of CAM therapies in the UK.

CAM therapy	Rationale	Treatments	Evidence
Aromatherapy	Operant conditioning Limbic stimulation Anticonvulsant properties of essential oils	Aromatherapy massage, pairing the smell of essential oils with a relaxed state. Once the pairing is achieved the smell of the oil itself may invoke the relaxed state, or 'divert' a seizure via limbic stimulation	One controlled trial with encouraging results ² CAUTIONS: Some essential oils may have proconvulsant properties, including rosemary, fennel, sage, hyssop and wormwood
Ayurvedic medicine	Based on ancient medical texts revealed to wise men by Brahma, the God of creation, approximately 6000 years BC. Ayurvedic understanding invokes three elements or humours within the human body: vata (air), pitta (bile), and kapha (phlegm). Imbalances between the elements are thought to be the source of illness and disease. Epilepsy is conceptualised as a psychiatric disorder	All treatments start with purging of the system with emetics and laxatives. Herbal treatments may be mixed with animal-based products in bespoke preparations	Laboratory studies indicate anticonvulsant properties in some plant remedies used No well controlled trials of ayurvedic medicines in patient populations CAUTIONS: Radical purging can cause status epilepticus in people with epilepsy taking anticonvulsants. Very high levels of arsenic, lead and other poisons have been found in some ayurvedic preparations ³
Chiropractic manipulation	The spine is involved in most illnesses, because it connects the head to the body. Misalignments in this core connection cause problems in distant parts of the body. Correcting these misalignments will result in a resolution of the symptoms	Spinal manipulation	No evidence supporting the therapy in epilepsy CAUTIONS: Well documented case studies of seizures, stroke and death following interruptions of the cerebral blood supply after neck manipulations
Cranial sacral therapy	Based upon the belief that the cranial bones can be moved with fingertip pressure and that this will alleviate the 'ratcheting' rhythms that cause epilepsy	Fingertip massage of the skull with very light pressure	Unscientific rationale No evidence supporting the therapy in epilepsy Some evidence discrediting the entire approach

Continued

Table 1. (Continued)

CAM therapy	Rationale	Treatments	Evidence
Herbal remedies	Based on the anticonvulsant properties of some plant products	Preparations containing plant products The scientific evaluation of plant properties is an up-and-coming area in the development of new antiepileptic treatments	Laboratory support for the anticonvulsant properties of some plants CAUTIONS: Unregulated market Toxicity Interactions with AEDs
Homeopathy	Based on the belief in a 'law of similars' or 'let like be cured by like'. If a substance in large doses produces specific symptoms, the same substance will, in extremely small doses, cure them. In direct contrast to modern medicines, homeopaths believe that the more dilute a substance is, the more potent it will be	Illnesses are treated with highly dilute preparations. The remedy prescribed will be chosen specifically for the individual as a whole, based on the homeopath's understanding of the patient's mind, body and spirit. As a result different people with the same condition may be prescribed different remedies	Anti-scientific rationale. The existence of molecules means that dilution cannot be infinite Nevertheless the individualised treatment regimen can create a powerful placebo effect with real effects resulting from associated reductions in stress, anxiety and low mood
Meditation	Meditation is a form of contemplation that manipulates attention. Most techniques require complete stillness and an exclusive mental focus on one thing, such as a single featureless object, the act of breathing, or the repetition of a single word, as in the recitation of a mantra. This eventually results in a 'loss of active attention', or a state of inattention. This state is sometimes called 'superconsciousness'	The attentional changes that occur during meditation are associated with EEG changes. Fast, synchronised brain waves have been recorded in people in deep meditation, and these patterns remain faster, even following the meditation, than those seen in people who do not meditate	Deep and repeated meditation clearly has the capacity to change EEG patterns, but it is unclear whether these changes make a seizure more or less likely to occur CAUTIONS: The high-amplitude gamma activity in some experienced meditators is the highest reported in a non-pathological context ⁴

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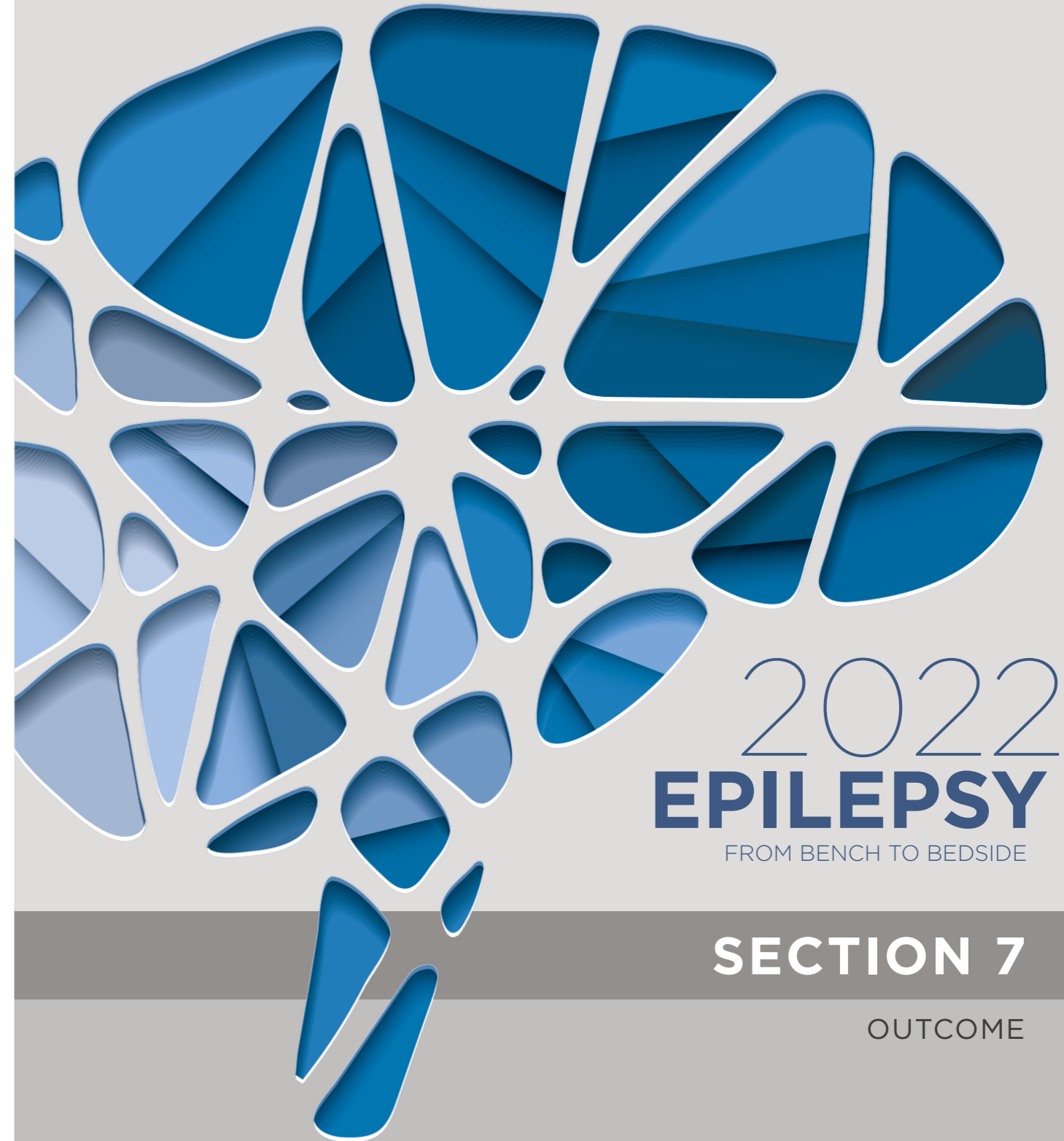
Table 1. (Continued)

CAM therapy	Rationale	Treatments	Evidence
The Mozart effect	Certain pieces of music appear to influence EEG patterns. In music theory, periodicity is a predictability that gives rise to expectations of what is coming next	Listening to Mozart's piano sonata in D major K.448 (a piece with high periodicity) either when the patient perceives an aura or more commonly on a regular basis, either in morning or in the evening	EEG changes have been recorded in group studies. Some support from well controlled case studies and small group series ⁵⁻⁸ NOTE: Carbamazepine may influence the perception of pitch in people with musical training. This appears to be reversible if the drug is discontinued. Distorted pitch perception associated with carbamazepine may go unnoticed in the majority of people with epilepsy who are not musically trained. However this peculiarly subtle effect of carbamazepine should be monitored in people who need perfect pitch perception for their work or musical pursuits
Oxygen therapy	Hyperbaric oxygen chambers increase the supply of oxygen to the brain. They have proven efficacy in the treatment of decompression sickness and can promote wound healing	Usually a series of daily or weekly sessions from 30 minutes to 1 hour	This treatment approach is associated with much hype on the internet. It appears to have originated from an unverified abstract of a study presented at a Chinese conference in 1987 CAUTIONS: Experimental work suggests that oxygen therapy increases the likelihood of seizures

Continued

Table 1. (Continued)

CAM therapy	Rationale	Treatments	Evidence
Traditional chinese medicine (TCM)	TCM is a complex, holistic system of medicine. TCM is based on the concept of a life force (Qi or Chi) and of balance (Yin and Yang). It invokes the concept of five basic elements in understanding health: wood, fire, earth, metal and water. All are thought to be in constant flux. The five elements theory is used to interpret the relationship between the health of the human body and the natural environment	The principal of differentiation guides diagnosis and treatment in TCM. In epilepsy, this process of differentiation extends beyond the clinical signs considered in Western medicine and involves a detailed examination of all aspects of an individual's lifestyle and emotional health, resulting in an individualised treatment plan from the outset. Medication may be based on one herb as the basic drug to treat the disease which is then mixed with other herbs to create a multifunction formulation. Acupuncture and tuina (therapeutic massage based on theories of acupressure points) may also be offered	TCM herbal remedies and acupuncture have been the subject of Cochrane Reviews. ⁹⁻¹⁰ The authors concluded that 'The current evidence is insufficient to support the use of traditional Chinese medicine as a treatment for epilepsy' CAUTIONS: Chinese herbal medicines involve plants, minerals and animal products. Some are simply described in the literature as anti-epilepsy capsules. It is not always clear what the medication contains. Some have been found to contain phenobarbital, phenytoin and other mainstream AEDs. This can lead to potentially serious consequences if the medication is abruptly stopped, or the formulation is changed



2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 7

OUTCOME

CHAPTER 36

The prognosis of epilepsy

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For patients with seizures, prognosis means the probability of further seizures after a single unprovoked seizure or the likelihood of achieving seizure freedom or terminal remission after a pattern of recurring seizures has been established¹. It is now accepted that up to 70–80% of people with epilepsy will enter remission, usually in the early years of the condition, with a smaller proportion achieving later remission². Nevertheless, in discussing the prognosis of epilepsy, various aspects need to be considered: the likelihood of recurrence following a single seizure, the impact of early versus late treatment, the probability of relapse after prolonged remission, the probability of seizure freedom following epilepsy surgery or relapse following antiepileptic medication withdrawal.

Recurrence after a single unprovoked seizure

Prospective studies of single seizures are difficult, as many events go unrecognised or are unwitnessed and patients do not usually present to medical attention unless the seizure is convulsive. The overall risk of recurrence following a single seizure has been reported to be 27–71%. A meta-analysis found that the average risk of seizure recurrence was 40% in prospective studies and 52% in retrospective studies³. The time interval between the seizure and inclusion in the follow-up influences recurrence, as many patients have a recurrence within weeks of the first seizure and are therefore classified as having epilepsy. This artificially lowers the estimated recurrence rate following a single seizure if there is a long delay between the initial seizure and recruitment into a recurrence study⁴. The risk of subsequent seizures decreases with time, with up to 80% of recurrences occurring within two years of the initial seizure³.

In the community-based study National General Practice Study of Epilepsy (NGPSE), 67% of those with a single seizure had a recurrence within 12 months and 78% within 36 months⁵ which, while high, is within the reported range. In the final analysis of the NGPSE cohort data, of those with a single seizure at presentation, 184/302 (61%; 95% CI 55% to 66%). The probability of remaining seizure free at 5 years following a single seizure was 0.37 (95% CI 0.33 to 0.41), 0.33 (95% CI 0.29 to 0.37) at 10 years, 0.32 (95% CI 0.28 to 0.35) at 15 years, 0.31 (95% CI 0.28 to 0.35) at 20 years and 0.29 (95% CI 0.26 to 0.33) at 25 years⁶. In a prospective study of children with a first unprovoked seizure, 45% had a second seizure with the median time to recurrence being 6.2 months. The cumulative risk of a second seizure was 22% (six months), 29% (one year), 37% (two years), 43% (five years) and 46% (ten years)⁷. Another prospective study of adults with a single seizure found a recurrence rate of 58% at 750 days' follow-up. No further recurrences were recorded thereafter during a median follow-up of 10.3 years, underlying the impression that the risk of seizure recurrence highest in the first 1–2 years following the seizure⁸.

Recurrence after a second seizure

The risk of recurrent seizures following a second seizure was investigated in a predominantly adult population⁹. The risk of a further seizure was 32% at three months, 41% at six months, 57% at one year and 74% at four years. Of those who did not have a recurrence after the second seizure within the first four years of follow-up, none had a relapse in the subsequent three years. The majority of those with a third seizure had a further seizure, with 31% of people who already had three seizures going on to have a fourth seizure at three months, 48% at six months, 61% at one year and 78% at three years. As with single seizures, the risk of further seizures is highest immediately after the last one. Similarly for children, the risk of a third seizure was 57% at one year, 63% at two years and 72% at five years after having a second seizure⁷.

Table 1. Long-term prognosis studies in epilepsy.

Country	Number	Follow-up (years)	Proportion 5YR TR (%)	Proportion 5YR TR off AEDs (%)	Study design
UK ⁶	N=657	23.6	82%	76%	Prospective (P)
USA ¹³	N = 457	20	70%	50%	Historic incident cohort
Japan ¹⁴	N = 1868	10	58.3%	N/A	Retrospective multi-institutional study
UK ¹⁵	N = 194	12	64%	40%	Retrospective (P)
Japan ¹⁶	N = 730	10-15	79.1%	N/A	Retrospective (P)
Japan ¹⁷	N = 143	18.9	62.8%	54.7%	Retrospective (P)
Sweden ¹²	N = 107	10	64%	17.5%	Prospective (All >17 years)
Finland ¹⁸	N = 144	40	67%	58%	Prospective (P)
Holland ¹⁹	N = 413	14.8	70.9%	61.9%	Prospective (P)

P = Paediatric study; 5YR TR = 5-year terminal remission rate

Short- and medium-term prognosis

In a prospective study of children with newly diagnosed epilepsy followed up from the time of diagnosis, 74% had achieved a period of remission (≥2 years' seizure freedom), of whom 24% had a further seizure. In those who had a relapse, approximately 50% occurred when an antiepileptic drug (AED) was being withdrawn or had been stopped⁹. In the NGPSE after nine years, 86% had achieved a remission of three years and 68% a remission of five years. The proportion in terminal remission by nine years was 68% for three years and 54% for five years¹⁰. In a study of patients aged ≥17 with newly diagnosed epilepsy, at ten years' follow-up the cumulative remission rates were 68% (one year), 64% (three years) and 58% (five years)¹².

Long-term prognosis

Few studies have looked at the long-term prognosis of people with epilepsy and most are retrospective and in paediatric cohorts (see table 1). In the Rochester study¹³, 65% had achieved a five-year period of remission at ten-year follow-up and 76% at 20 years. At ten years after diagnosis 61% were in terminal remission with 70% in terminal remission at 20 years. Of those in remission, 20% continued on AEDs while 50% had successfully discontinued medication and remained seizure-free for ≥5 years. In a cohort of children with active epilepsy followed up for 12 years 64% were in terminal remission (defined as ≥3 years seizure free) after 12 years¹⁵. In the NGPSE cohort, after a median duration of follow-up of 23.6 years, in 327 people with complete follow-up, 268 (82%; 95% CI 77% to 86%) were in terminal remission (i.e. no seizures in the previous five years) and 204 (76%; 95% CI 71% to 81%) were in terminal remission and off AEDs⁶.

In a study of children followed up for an average 37 years, 67% were in terminal remission, on or off medication. Early remission, defined as remission occurring within the first year of treatment, was achieved by 31%, and the remission continued to terminal remission in half of these. Remission without relapse occurred in 50% with a mean delay of nine years. A total of 14% entered remission but subsequently relapsed with further remission, indicating a relapse-remitting pattern, while 19% continued with seizures from the onset¹⁸. Of children followed up for a median of 40 years, 93% had one or more periods of remission (one year), emphasising the overall excellent prognosis of childhood epilepsy²⁰.

For those with chronic epilepsy, up to one-third will have a relapsing remitting pattern with at least one period of significant seizure freedom²¹.

Prognostic factors

Many studies have looked at possible predictors of seizure prognosis, including age of onset, gender, aetiology, seizure type, EEG patterns, number of seizures prior to treatment and early response to treatment²². In patients presenting with a first-ever seizure, the presence of multiple discrete seizures within 24 hours is not associated with a worse prognosis than those with a single seizure²³. Remote symptomatic epilepsy, the presence of a neurological birth deficit and learning disability are consistently shown to be associated with a poorer prognosis. In one study the three-year remission rate was 89% for those with idiopathic epilepsy and normal examination compared to only 49% in those with a neurological deficit or learning disability¹⁴. The number of seizures in the first six months after onset has been found to be a strong determinant of the probability of subsequent remission, with 95% of those with two seizures in the first six months achieving a five-year remission compared with only 24% of those with more than ten seizures²⁴.

Seizure type has been an inconsistent prognostic factor with some studies indicating that those with partial seizures have a poorer prognosis¹³ while other studies have demonstrated a poorer prognosis for those with generalised onset seizures²⁵. People with multiple seizure types, as is typical in the childhood encephalopathies, appear to have a poorer prognosis²⁶. A significant reduction or complete cessation of seizures within three months of initiating treatment has been shown to be a strong predictor of subsequent remission²⁷. The probability of seizure remission decreases significantly with each successive treatment failure. Only 11% of patients who discontinued the first appropriate AED due to lack of efficacy became seizure free on a second AED and only 4% on a third medication or on polypharmacy²⁸.

Children who experience clusters of seizures during treatment are much more likely to have refractory epilepsy than children without clusters and are less likely to achieve five-year terminal remission²⁹. Children who continued to have weekly seizures during the first year of treatment had

an eight-fold increase in the risk of developing intractable epilepsy and a two-fold increase in the risk of never achieving one-year terminal remission²⁰.

The impact of aetiology on prognosis

When comparing prognosis by aetiology, patients with idiopathic generalised epilepsy appear to have a better prognosis than patients with symptomatic or cryptogenic partial epilepsy. In one study 82% of people with idiopathic generalised seizures achieved one-year seizure freedom compared to only 35% with symptomatic partial epilepsy and 45% with cryptogenic partial epilepsy²⁹. Temporal lobe epilepsy (TLE) is associated with a poorer prognosis than extra-temporal lobe epilepsy^{30,31}.

For patients with a single identified lesion, TLE with hippocampal sclerosis (HS) had a particularly bad prognosis (11% seizure free) compared with other aetiologies (24% with cortical dysplasia seizure free). Patients with HS and another identified pathology (dual pathology) had the worst prognosis (3% seizure free)³⁰. In another study no difference in prognosis between those with symptomatic and cryptogenic partial epilepsy was found³¹. Comparing patients by aetiology, they found that mesial TLE had the worst prognosis compared to rates for other aetiologies³¹.

The impact of medication on prognosis

In the Western world most patients are commenced on AED after two unprovoked seizures, implying that prognostic studies from Western countries are essentially those of treated epilepsy. Evidence from studies from resource-poor countries where a significant treatment gap exists suggests that many patients may enter spontaneous remission with no AED³¹.

Indeed the response to AEDs in patients with chronic long-standing epilepsy is comparable to that of patients with new-onset seizures^{32,33}. Such evidence contradicts the belief that epilepsy is a chronic progressive condition unless early treatment is commenced³⁴. It has been suggested that patients with epilepsy can be subdivided into prognostic groups based on their aetiology and epileptic syndrome. This important concept implies that the need and response to antiepileptic treatment in epilepsy is determined by the different prognostic groups^{1,2}.

Early versus late treatment

Two studies have assessed the impact of medication on the risk of seizure recurrence. In the FIRST study, patients with first unprovoked generalised seizures were randomised to either immediate treatment (treated group) or to treatment only after a further seizure (untreated group). While immediate treatment reduced the risk of early relapse, it did not affect the long-term prognosis, with comparable five-year remission rates in the two groups³⁵.

In the MESS study patients with a single seizure or early epilepsy (all types) were randomised to receive immediate or deferred treatment. Patients in the immediate treatment group had increased time to first and second seizure and first generalised seizure, in addition to having a reduced time interval to two-year remission. At five years' follow-up, however, 76% in the immediate group compared to 77% in the deferred group had achieved 3–5 years' seizure freedom³⁶.

In conclusion, immediate treatment delays the early recurrence of seizures but does not affect the medium- or long-term prognosis.

Prognosis following AED withdrawal

In the largest randomised controlled trial of continued treatment vs drug withdrawal in 1013 patients in remission (two or more years seizure free), at two years post-randomisation 41% of those who had discontinued medication had had a recurrence of seizures compared to 22% of those who stayed on medication. The difference in relapse rates between the two groups was maximal at nine months, with the rate of relapse higher in the discontinuation group up to two years' follow-up, but by 2–4 years the risk of relapse was higher in those continuing treatment³⁷. Patients who experienced a relapse were followed up, and by three years 95% had a further one-year remission and by five years 90% had had a further two-year remission period, indicating that the long-term prognosis was similar in both groups³⁸.

A further analysis of the data from the MRC AED withdrawal study using regression modelling has recently been reported³⁹. The recurrence risk within the first 12 months following AED withdrawal was 30% (95% CI 25–35) while the risk of recurrence within the next 12 months three months after AED withdrawal was 15% (95% CI 10–19). For those who had a seizure recurrence, three months after recommencing treatment the risk of seizure recurrence within the next six months was 18% (95% CI 10–27) and 26% (95% CI 17–35) within 12 months³⁹.

An analysis of 14 AED withdrawal studies found that the recurrence rate following AED discontinuation ranged from 12–66% (mean 34%) and reinstatement of treatment was successful in obtaining further remission in, on average, 80% with no significant differences between age groups. A second remission may, however, take many years to achieve, while in an average of 19% the reintroduction of the medication did not control the seizures as before. Up to 23% of those discontinuing treatment go on to develop intractable epilepsy. Risk factors for subsequent poor treatment outcome were symptomatic partial epilepsy and cognitive deficits⁴⁰.

Despite the risk of seizure recurrence, patients may choose to discontinue treatment because of the impact of continuing antiepileptic medication on quality of life. In one study⁴¹, the effect of AED withdrawal on quality of life was assessed. At one year seizure recurrence had occurred in 15% of the withdrawal group compared with 7% in the non-withdrawal group. The proportion of patients having completely normal neuropsychological findings increased from 11% to 28% in the withdrawal group while decreasing from 11% to 9% in the non-withdrawal group. No differences in quality of life were observed between the two groups. At 41 months' follow-up, predictors of continued seizure freedom following treatment withdrawal were prior use of carbamazepine (approximately three-fold increase in likelihood of remaining seizure free compared with patients on any other drug) and a normal neurological examination⁴¹.

Prognosis following epilepsy surgery

Only two randomised controlled trials have compared the outcomes of patients with temporal lobe epilepsy randomised to either surgery or continued medical treatment^{42,43}, the latter study being of somewhat limited value due to difficulty recruiting suitable patients for inclusion in the study⁴³. In the earlier study, 80 patients with temporal lobe epilepsy were randomised to have either epilepsy surgery or continued medical treatment for one year. A total of 90% of patients in the surgery group underwent surgery with 64% free from seizures impairing consciousness (42% completely seizure free) compared to 8% (3% completely seizure free overall) in the medical group at one year. Quality of life was also improved in patients after surgery compared to patients in the medical group ($P < 0.001$)⁴².

In a recent review of controlled studies (total 2734 patients, all but one study non-randomised) 44% of patients in the surgical group (mainly temporal lobe surgery) were seizure free compared

to 12% with medical treatment only. Moreover surgical patients were four times more likely to be able to discontinue medication compared to non-surgical patients⁴⁴.

In the long-term follow-up of 615 adults who underwent epilepsy surgery (497 anterior temporal resections, 40 temporal lesionectomies, 40 extratemporal lesionectomies, 20 extra-temporal resections, 11 hemispherectomies, and seven palliative procedures [corpus callosotomy, subpial transection]), patients who had extra-temporal resections were more likely to have seizure recurrence than were those who had anterior temporal resections (hazard ratio [HR] 2.0, 1.1–3.6; $P = 0.02$). The longer a person remains seizure free the less likely they would relapse, while conversely the longer seizures persisted post-operatively the less likely seizure remission would be achieved⁴⁵.

In summary, in appropriately selected patients, surgery is four times more likely to render patients seizure-free than medical treatment alone.

Prognosis in those with intractable epilepsy

Studies suggest that failure to control seizures with the first or second AED implies that the probability of subsequent seizure control with further AEDs is slim²⁸. This can lead to clinical nihilism when dealing with such patients in clinic. A recent series of papers suggests, however, that such a view is overly pessimistic. In a retrospective analysis of the effect of 265 medication changes in 155 patients with uncontrolled epilepsy of at least five years' duration, 16% of all patients were rendered seizure free (12 months or more) following a drug introduction while a further 21% had a significant reduction of seizure frequency. Overall 28% of the cohort was rendered seizure free by medical changes⁴⁶.

In another study a group of 246 patients with refractory epilepsy was followed for three years. Excluding those who became seizure free because of surgery, 26 (11%) became seizure free (six months' terminal remission) as a result of medication change (addition of a new AED or dose change). No single AED was associated with a statistically significant probability of inducing seizure freedom. Patients with mental retardation were statistically less likely to achieve a remission. Overall approximately 5% per year became seizure free, highlighting the fact that, irrespective of the number of AEDs previously tried, there is still a possibility of inducing meaningful seizure remission in this population⁴⁷.

The probability of seizure relapse following remission was retrospectively studied in a cohort of 186 patients with intractable epilepsy who were followed for a median of 3.8 years. Overall 20 patients achieved a remission of ≥ 12 months with a 4% probability of remission per year. Of these, five subsequently suffered a relapse with the estimated cumulative probability of relapse 33% at two years and 44% at three years. No clear predictors of remission or subsequent relapse were identified⁴⁸.

In summary, approximately 4–5% a year of those with refractory epilepsy will achieve a remission of 12 months on medication, although more long-term follow-up demonstrates that approximately one-half will subsequently relapse⁴⁹.

Conclusions

The overall prognosis for people with newly diagnosed epilepsy is good, with 70–80% becoming seizure-free, many of whom doing so in the early course of the condition. The probability of obtaining seizure freedom is particularly high in those with idiopathic generalised epilepsy and normal neurological examination. For those who continue to have seizures despite multiple

appropriate AED treatments, in appropriate candidates epilepsy surgery is four times more likely to render seizure freedom than continued medical treatment alone. Despite this, medical changes will achieve a remission of 12 months in 4–5% a year of those with seemingly intractable epilepsy.

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CHAPTER 37

The mortality of epilepsy

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It has been consistently shown in population studies that the risk of premature death is two to three times higher in people with epilepsy than in the general population. This mortality risk is highest in the early years following diagnosis. The risk is stratified by aetiology with people with remote symptomatic epilepsy and neurological deficits having persistently higher risks. Other factors of relevance have been gender, age, a previous episode of status epilepticus, frequency and severity of seizures and antiepileptic drug (AED) compliance.

Long-term population-based prospective incident cohort studies provide the most reliable means of examining the risk of premature mortality and the way it changes over the course of the condition¹, although there are very few studies with follow-up of more than 20 years.

The estimates of the risk of premature death have varied between studies, and case ascertainment can be an issue depending on the methodology used. Mortality studies in epilepsy should be community-based studies of incident cohorts. Studies of people with prevalent epilepsy may underestimate the short-term mortality (as the mortality in people with epilepsy has consistently been shown to be highest in the early years following diagnosis) while simultaneously overestimating the long-term mortality (as those who have gone into remission may not be included in the cohort)². The risk of premature death in people with epilepsy has been studied using death certificates, hospital or institutional records and through follow-up of community cohorts. Death certificates have been shown to be an unreliable source, with epilepsy being recorded on the death certificate in only 7% of patients known to have had seizures³. This figure increased to 17% in those with frequent seizures. In a community-based study of mortality in children with epilepsy, epilepsy was recorded on the death certificate in 55% of deaths directly attributable to epilepsy⁴.

The most commonly reported measures of mortality in epilepsy studies comparing deaths between the study and a control population are the proportional mortality ratio (PMR) and the standardised mortality ratio (SMR). The PMR gives the proportion of deaths caused by a specific cause in the cohort and compares it with a control group. This is not a direct measure of mortality but rather gives the proportion of deaths due to one specific cause and can be influenced by the rates of other causes of death. The SMR is the ratio of the observed deaths in the study population to the expected deaths if the group had experienced the same age and sex-specific death rates as the population from which they came.

What is the risk and who is at risk?

Studies have consistently shown that males with epilepsy have higher mortality rates, with no clear explanation for this difference. The SMR tends to be high in children but this relates principally to the underlying cause of the epilepsy (remote symptomatic, perinatal insults) rather than to the epilepsy itself. The lowest SMRs are reported in the 75+ age group; this relates in part to the fact that this age group in the population has a high mortality rate.

Few studies have looked at the risk of mortality after a single seizure. Two retrospective studies have investigated mortality after a single unprovoked seizure; one provided an SMR of 2.3 (95% confidence interval [CI] 1.5, 3.3)⁵ and the other an SMR of 1.1 (95% CI 0.1, 4.0) for single idiopathic seizures⁶. In the NGPSE, people with an acute symptomatic seizure (provoked seizure) had an SMR of 3.2 (CI 2.4, 4.3) after more than 20 years of follow up⁷. Overall the SMR in people with a newly diagnosed unprovoked seizure ranges from 2.5 to 4.1 with the highest rates in children and those with symptomatic aetiology⁸.

Reported SMRs in mortality studies from developed countries range from 1.6 to 4.1⁹. In the Rochester study⁵, the SMR for the total group after 29 years' follow-up was 2.3, with the most significant increase in the first 10 years. In the NGPSE the SMR was 2.5 after median 6.9 years with the highest SMR in the first year (5.1)¹⁰. The SMR further decreased to 2.1 after 11 to 14 years of follow up¹¹, and remained stable but persistently elevated after a median follow-up of 22.8 years⁷. The highest SMRs were estimated in people with remote symptomatic epilepsy (SMR 3.7; 95% CI 3.1, 4.6) and epilepsy due to a congenital neurological deficit (SMR 19; 95% CI 7.0, 49.7)⁷, which remained elevated throughout follow-up. In contrast people with idiopathic/cryptogenic epilepsy (defined as aetiology not determined) did not have a significantly increased long-term mortality rate (SMR 1.3; 95% CI 0.9, 1.9)¹¹ in the initial stages of follow-up, a finding that has been replicated in community-based studies in Iceland⁶ and France¹². The French study, which examined the short-term mortality in people with epilepsy, is the only study to have used the categories idiopathic and cryptogenic epilepsy as defined by the ILAE, with no significant differences between the two groups. Interestingly, mortality was significantly elevated in people with idiopathic/cryptogenic epilepsy in the NGPSE during the last 10 years of follow-up⁷.

Data on premature mortality in people with epilepsy from resource-poor countries is more limited. Findings from a prevalent cohort study with a follow-up of 6.1 years gave an overall SMR of 2.9 (95% CI 2.6, 3.4)¹³, although the SMR reported earlier, after the first 25 months of follow-up, was higher (SMR 3.9, 95% CI 3.8, 3.9)¹⁴. A much higher SMR was found in young people (aged 10–29 years) (SMRs 28 to 37). Death from drowning was a significant risk (overall SMR 39; 95% CI 26.4, 55.5), but was more critical for people living in a waterside area than for those living in the mountains (HR 3.9; 95% CI 1.7, 9.2, $P = 0.002$)¹⁴. A similar prevalent cohort with a follow-up of median 28 months found an overall SMR of 4.9 (95% CI 4.0, 6.1), with higher SMRs in young people¹⁵.

Overall, people with epilepsy have been found to have a reduction of life expectancy which is greatest at the time of diagnosis. This reduction can be up to two years in people with idiopathic/cryptogenic epilepsy and up to 10 years in people with symptomatic epilepsy¹⁶.

Mortality in population-based studies is summarised in Table 1.

Causes of death

Causes of death in people with epilepsy can be divided into epilepsy-related and non-epilepsy-related deaths (see Table 2). For people with symptomatic epilepsy (both remote and progressive) the excess mortality risk relates primarily to the underlying cause of the epilepsy rather than to the epilepsy itself. In a study of 692 children with epilepsy followed up over an average of 13 years, the SMR was 5.3, with functional neurological deficit being the only independent predictor of mortality (occurring in 85% of cases)¹⁷.

In a Finnish cohort of 245 children with epilepsy identified between 1961 and 1964 and followed up prospectively, 44 had died by the follow-up in 1992. Of these 75% had remote symptomatic epilepsy¹⁸ (similar to that found in childhood mortality studies from Australia⁴ and Nova Scotia¹⁷). Most (89%) of those who died were not in remission at the time of death, with a relative risk of

death in those with active epilepsy compared with those in remission of 9.3 (95% CI 3.8, 22.7). The cause of death was definitely or probably related to a seizure in 45% of cases. There were three cases of sudden unexplained death in epilepsy (SUDEP) in people with idiopathic epilepsy, none of whom was in remission at the time of death¹⁸. In the extended follow-up of the cohort up to 2002, 60 (24%) had died, of whom 51 (85%) were not in terminal remission (≥ 5 years seizure free) at the time of death. Those with a remote symptomatic aetiology were three times as likely to die as those with idiopathic/cryptogenic aetiologies (37% vs 12%). Of the 60 deaths, 33 (55%) were felt to be epilepsy related, including 18 deaths from SUDEP, giving a cumulative risk of SUDEP of 7% at 40 years (12% for those not in terminal remission and not taking AEDs¹⁹).

Table 1. Population studies of mortality in people with epilepsy with standardised mortality rates (with 95% confidence intervals).

Country	SMR	Ages	Comments
Poland ²⁰	1.8	All	Retrospective prevalent cohort
United States ⁵	2.3 (1.9, 2.6)	All	Historic incident cohort (Rochester)
United States ²¹	2.1 (1.9, 2.5)	All	SMR for IHD elevated in those <65 years
Iceland ⁶	1.6 (1.2, 2.2)	All	Historic incident cohort
France ¹²	4.1 (2.5, 6.2)	All	Prospective, incident cohort 1 yr mortality
Sweden ²²	2.5 (1.2, 3.2)	³ 17 years	Prospective incident cohort with first seizure
Canada ¹⁷	5.3 (2.3, 8.3)	<17 years	Historic incident cohort
China ¹³	2.9 (2.6, 3.4)	>2 years	Prospective prevalent cohort
United Kingdom ⁷	(2.2, 2.9)* 2.2 (2.0, 2.5)**	All	Prospective incident cohort (NGPSE) 1984-2009

*definite epilepsy **definite and possible epilepsy

In a Dutch study of mortality in people with epilepsy followed for over 40 years the SMR was 16 in the first two years decreasing to 2.8 thereafter²⁴. After two years, approximately one-third of deaths were directly or indirectly attributable to epilepsy. Common non-epilepsy causes of death cited in mortality studies include pneumonia, cerebrovascular disease, malignancy and heart disease. SMRs and PMRs are consistently elevated for these causes in population-based studies and often markedly so in the first few years of follow-up. In a Swedish study looking at cause-specific mortality in over 9000 adults with epilepsy, the overall SMR was 3.6 (95% CI 3.5, 3.7), with SMRs being increased for specific causes such as cancer (SMR 2.6; 95% CI 2.4, 2.8), respiratory disease (SMR 4.0; 95% CI 3.6, 4.5), heart and cerebrovascular disease (SMR 3.1; 95% CI 3.0, 3.3) and accidents and poisoning (SMR 5.6; 95% CI 5.0, 6.3)²⁵. The risk of premature death from heart disease in people with epilepsy was found to be elevated in those aged 25 to 64 but not for those aged 65 years and over in the Rochester cohort²¹, and also in the NGPSE cohort during the last five years of follow-up⁷. Bronchopneumonia is an important cause of mortality in people with epilepsy of all ages, not just the elderly, and was associated with the highest SMR (6.6) in the NGPSE⁷. This

may be related to aspiration during seizures although this is unproven since a significant proportion of the cohort had gone into terminal remission. Patients may have been more prone to infections due to the chronic effects of seizures on the immune system²⁶ or may have been the terminal event.

Table 2. Causes and categories of death in epilepsy²³.

Epilepsy-related deaths	
	SUDEP
	Status Epilepticus
	Drowning
	Trauma / Motor accidents
	Falls, burns, asphyxiation
	Aspiration Pneumonia
Deaths related to underlying disease	
	Primary and secondary CNS neoplasia
	Cerebrovascular disease
	CNS infections
	Inherited neurodegenerative disorders
Treatment-related deaths	
	Idiosyncratic drug reactions e.g. fulminant liver failure, aplastic anaemia
	Drug toxicity
Deaths indirectly or unrelated to epilepsy	
	Pneumonia
	Suicide
	Ischaemic heart disease
	Non-CNS neoplasia

The influence of mental retardation (MR) and epilepsy was investigated in a Swedish study. The SMR was 1.6 (95% CI 1.3, 2.0) in people with MR only but this increased to 5.0 (95% CI 3.3, 7.5) for those with MR and epilepsy, with the increase in mortality associated with seizure type and frequency²⁷. In studies from institutions and hospitals, where people have presumably more severe epilepsy, epilepsy-related deaths are more common. In one study, PMRs were cancer (26%), bronchopneumonia (25%), circulatory diseases (24%), seizure-related deaths (other than SUDEP) (12%) and SUDEP (6%)²⁸.

SMRs and PMRs for cancer have been consistently elevated in people with epilepsy even after excluding CNS neoplasms. Studies are however limited by the need for long follow-up periods and

confounders such as potential differences in lifestyle. Cancer mortality was compared between two cohorts with epilepsy, one from an institution with more severe epilepsy (SEC) and the other, a community-based population with milder epilepsy (MEC). The SMR for all cancers was elevated in the SEC (SMR 1.42; 95% CI 1.18, 1.69) but not in the MEC (SMR 0.93; 95% CI 0.84, 1.03). The SMR for brain and CNS neoplasms was significantly elevated in the group with milder epilepsy²⁹. Various putative mechanisms for the high SMRs for non-CNS neoplasia have been proposed. A carcinoma-promoting effect has been seen in rodent models, with an association observed between phenobarbital and liver tumours³⁰; and lymphoid cell and liver tumours with phenytoin³¹. Both drugs are considered possibly carcinogenic in humans although pharmaco-epidemiological data is inconsistent. Newer antiepileptic drugs have shown no evidence of carcinogenicity either during regulatory testing or post-marketing surveillance. Survival rates in cancer can be reduced by the concomitant use of enzyme-inducing AEDs through increased hepatic clearance of cytotoxic agents³².

Two recent studies from Finland³³ and Austria³⁴ have looked at cause-specific mortality in people with epilepsy, and both demonstrate that the majority of deaths are due to non-epilepsy-related causes. In the Finnish study³³, which was based on a nationwide register-based cohort study of people aged 10 years or older diagnosed with epilepsy between 1990 and 1994, the predominant causes of death were CNS cancer (17%), other cancers (15%), ischaemic heart disease (11%) and cerebrovascular diseases (10%), which may have been related to the probable underlying aetiology. In contrast the proportion of deaths attributable to epilepsy was small with 3.9% of deaths attributable to accidents, 3.4% for alcohol-related diseases and 1.6% for suicides.

Vascular disease is an important non-epilepsy related cause of death in people with epilepsy. Epidemiological studies show that epilepsy is associated with an SMR of 1.2–2.5 for ischaemic heart disease³⁵. AEDs that enhance hepatic P450 cytochrome system activity have been associated with accelerated atherosclerosis through increased cholesterol synthesis, that can be reversed on switching to non-enzyme inducing AEDs³⁶. A possible gender effect is seen, with a more significant association seen with females. Non-enzyme inducing AEDs e.g. valproate can also increase vascular disease through promoting obesity seen in up to 71% of patients treated with valproate. Postulated mechanisms include appetite stimulation, changes in fatty acid metabolism, insulin resistance and the metabolic syndrome³⁷.

The risk of premature mortality is similarly elevated in people with drug-resistant epilepsy³⁸. In a prevalent cohort of 433 people with drug-resistant epilepsy (at least one seizure per month despite treatment with two or more AEDs), with median duration of epilepsy 25 years at study entry who were followed up for six years, the cumulative probability of death was 8.7% (95% CI 6.2, 12.1) with an overall SMR of 2.4 (95% CI 1.7, 3.3). The mortality was largely driven by those with a known epilepsy aetiology; the SMR was 3.1 (95% CI 2.0, 4.6) in people with a remote symptomatic or progressive aetiology and 1.7 (95% CI 0.8, 2.8) in people with an unknown aetiology). The excess mortality in those with known aetiology was not eliminated by exclusion of those with progressive aetiology (SMR 2.5; 95% CI 1.4, 3.8).

The portion of the NGPSE cohort with recurrent unprovoked seizures (N=558) was recently examined to investigate the immediate and underlying causes of death, and their relationships to epilepsy aetiology³⁹. Over almost 25 years of follow-up, 190 people (34%) died. Together non-cerebral neoplasm, cardiovascular and cerebrovascular disease accounted for almost 60% of deaths, while epilepsy-related causes accounted for only 3%. In almost one quarter (23%), the underlying cause of death was related to the aetiology of the epilepsy; this was more likely if death occurred in the first two years after seizure onset.

Epilepsy-related deaths

Deaths directly related to epilepsy include SUDEP, status epilepticus, consequences of seizures (including accidents, drowning and aspiration pneumonia) and iatrogenic (drug toxicity and idiosyncratic).

The case fatality following status epilepticus typically ranges from 10–22%⁴⁰ (Richmond 21%⁴¹), with some lower case fatality rates in Europe, possibly as a result of the exclusion of deaths due to status epilepticus following anoxic encephalopathy.

The primary determinant of prognosis in status epilepticus is aetiology⁴² but other factors such as age and seizure duration are important in determining outcome⁴³. There is some suggestion that the case fatality following status epilepticus may be decreasing (although the evidence is conflicting)⁴⁴ and is particularly low in children⁴⁵.

SUDEP is defined as a sudden, unexpected death in an individual with or without evidence of a seizure where post mortem does not reveal a specific cause of death⁴⁶. Estimates of SUDEP rates are heavily influenced by the population under study, with much higher rates in those with severe or refractory epilepsy. Identified risk factors for SUDEP include younger age of onset, long duration of epilepsy and refractory epilepsy⁴⁷. The incidence of SUDEP was 0.35 per 1000 person years in the Rochester cohort⁴⁸, while an incidence of 1:295 per year was found in children with more severe epilepsy and learning difficulties⁴⁹. SUDEP is reviewed in greater detail in Chapter 38.

People with epilepsy may die as a result of an accident during a seizure. Based on attendance records of four accident and emergency (A&E) departments, the risk of injury as a result of a seizure was estimated to be 29.5 per 100,000 population per year⁵⁰. Many seizure-related injuries tend to be minor, with an increased risk related to background seizure frequency⁵¹, but some injuries can be fatal.

In a one-year population-based study (using inpatient records, doctors' claims and A&E visits) the annual incidence of injuries was higher in people with epilepsy, with 20.6% of people with epilepsy having at least one injury compared with 16.1% among people without epilepsy ($P < 0.001$). In particular, people with epilepsy were more likely to have fractures, crushing injuries, intracranial and other head injuries⁵². Similarly over a two-year period, people with epilepsy were more likely to have injuries inflicted on them by others (odds ratio 1.46; 95% CI 1.04, 2.03) after adjustment for co-morbidities; they were slightly more likely to have motor vehicle accidents and completed or attempted suicide⁵³.

People with epilepsy have an increased risk of drowning (15- to 19-fold) compared with the general population. In a meta-analysis of the risk of drowning, the total SMR was 18.7. The SMR varied depending on the population under study, with an SMR of 5.4 in community-based incident cohorts, 18 in people with prevalent epilepsy, 25.7 in people with epilepsy and learning disability and 96.9 for people in institutional care⁵⁴.

People with epilepsy have been shown to be at increased risk of suicide in some studies^{13,20,25} but not in others⁵¹. In a meta-analysis, the SMRs for suicide in people with epilepsy were markedly elevated, particularly for those with temporal lobe epilepsy⁵⁵. In a population-based control study from Denmark, 2.3% of people with epilepsy committed suicide compared with 0.7% in the general population, corresponding to a three-fold increased risk (risk ratio 3.2; 95% CI 2.9, 3.5). This risk was particularly high in people with co-morbid psychiatric illness and in the first six months following diagnosis⁵⁶. A more recent meta-analysis found that the overall SMR for suicide in people with epilepsy was 3.3 (95% CI 2.8, 3.7), with the highest rates being in those following temporal

lobe excision (SMR 13.9), following other forms of epilepsy surgery (SMR 6.4) and in people with temporal lobe epilepsy (SMR 6.6⁵⁷).

In a study⁵⁸ looking at the role of psychiatric comorbidity in premature mortality in people with epilepsy, people diagnosed with epilepsy in Sweden between 1969 and 2009 were identified through the National Patient Register (n = 69,995) and compared with age-matched and sex-matched controls (n = 660,869) and unaffected siblings (n = 81,396) for risks and causes of premature mortality. During follow-up 6155 (8.8%) people with epilepsy died. A total of 972 people with epilepsy (15.8%) died from 'external causes' (suicide, accidents or assault) with a high adjusted odds ratio (aOR) for non-vehicle accidents (aOR 5.5; 95% CI 4.7, 6.5) and suicide (aOR 3.7; 95% CI 3.4, 4.2). While 75% of those who died from external causes had comorbid psychiatric disorders with strong associations in individuals with depression (aOR 13.0; 95% CI 3.16, 6.0) and substance abuse (aOR 22.4; 95% CI 18.3, 27.3) compared to people without epilepsy and no psychiatric comorbidity, the risk was also increased in people with epilepsy but no depression (aOR 3.3; 95% CI 3.0, 3.7) or substance abuse (aOR 2.2; 95% CI 1.9, 2.6).

AEDs and increased mortality

It has been suggested that antiepileptic treatment with more than two AEDs increases the risk of SUDEP⁵⁹, though other studies have not shown an increased risk of SUDEP with any AED in monotherapy or in combination therapy⁶⁰. Moreover, the risk of suicide in people taking AEDs, although increased, appears to be low⁶¹.

It has been reported that long-term use of AEDs is associated with an increased risk of fractures, particularly in women, with the risk increasing with the duration of treatment⁶².

The response to treatment has been suggested as a determinant of mortality, with people who continue to have seizures despite treatment having an increased risk of premature death compared with those rendered seizure free where no such risk was observed⁶³.

Non-adherence to antiepileptic medication has been shown to be associated with an over three-fold increased risk of death (hazard ratio 3.3; 95% CI 3.1, 3.5) after controlling for possible confounding factors. Non-adherence was also associated with 86% increased risk of hospital admission and a 50% increased risk of A&E attendance⁶⁴.

Conclusions

It is clear, a diagnosis of epilepsy is associated with an increased risk of premature death, particularly in the early years following diagnosis. The proportion of deaths due to epilepsy tends to be higher in selected population studies, affecting up to one third, compared with community studies. This risk is decreased but probably not eliminated by rendering the person completely seizure free. In population-based studies, the majority of epilepsy patients succumb to non-epilepsy related causes e.g. pneumonia, malignancies and vascular disease. Clinicians should therefore take the opportunity of counselling patients on the reduction of vascular risk and lifestyle modifications, particularly in high risk patients.

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CHAPTER 38

Sudden unexpected death in epilepsy**FERGUS J. RUGG-GUNN**

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SUDEP is defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicological cause for death¹. Where autopsy is not performed, and for the purpose of epidemiological studies, sudden death occurring in benign circumstances with no known competing cause for death is classified as 'probable SUDEP'. Despite an applicable definition, and clear guidance where there is uncertainty, significant variability in use has hampered efforts to integrate findings from multiple studies on epidemiological and risk factor data and hence establish common relevant factors^{2,3}.

Epidemiology

Sudden unexpected death in the general population is extremely rare in young adults with an incidence of 5-10/100,000 person-years, while the rate climbs steeply with advancing age to approximately 300/100,000 person-years in the elderly⁴. The incidence of sudden death in patients with epilepsy is significantly higher and varies markedly with the population studied⁵. For example, in population-based studies the incidence has been reported to be 0.35 and 2.7/1000 person-years depending on the methodologies employed^{6,7}. This increases to between 2 and 5.9/1000 person-years in cohorts of patients attending specialist epilepsy clinics⁸⁻¹⁰, 3.4/1000 person-years in pupils with epilepsy enrolled in a special residential school¹¹ and up to 9.3/1000 person-years in epilepsy surgery candidates^{12,13}. The incidence of sudden death in young adults with intractable epilepsy is therefore many times that of the general population, with a peak between the ages of 20 and 40 years¹⁴. In older age groups the relative increased incidence of SUDEP is too small to measure, and is confounded by the occurrence of co-morbidity such as cardiovascular, respiratory or cerebrovascular disease.

Risk factors

There is significant debate regarding risk factors for SUDEP. Relevant and independent risk factors are difficult to establish given the non-independence of patient, syndrome, seizures and treatment characteristics. Multiple logistic regression analyses require large cohorts of patients to achieve statistical significance for each of the variables evaluated and this is difficult to attain¹⁵. Furthermore, the high variability between studies in terms of patient cohorts, definition, choice of control group, methodology and overall study quality precludes not only a valid meta-analysis, but even a simple meaningful comparison.

Demographics

Descriptive studies have almost universally reported that patients with SUDEP are young adults^{6,7,9,10,16-20}. A number of biases exist however, including, by definition, the exclusion of patients with significant co-morbidity associated with increasing age, such as ischaemic heart disease

or cerebrovascular disease, identified on postmortem examination^{9,16,20}. Other examples of bias include case identification through self-referral by bereaved relatives, most commonly parents¹⁸, and studies with only small numbers of patients^{6,9}. Case-control studies are less conclusive. Some studies only included defined age groups and can draw no conclusions regarding other age groups. Nevertheless, it is interesting to note that 70-80% of the studied population in a number of case-control studies were less than 45 years old^{14,21}. Data regarding age, however, is not available from a number of large studies due to age-matching of control subjects^{14,21,22}.

Of the remaining studies, the use of a cohort of non-SUDEP deaths as a control group may bias the patient group towards a younger age due to exclusion of co-morbid conditions more commonly associated with advancing age²³⁻²⁶, although young age as an independent risk factor has not been universally reported^{27,28}. The likelihood of selection bias is corroborated by finding significantly less co-morbidity in the SUDEP group than the non-SUDEP group²⁶. In studies using living control subjects, younger age was not seen more frequently in the SUDEP group, although numbers of SUDEP patients were small⁸.

Although a large number of descriptive studies have suggested that male gender is a significant risk factor for SUDEP^{7,9,17,20,29}, this has not been confirmed by the vast majority of case-control studies^{21-23,26-28,24,30,34}. In addition, a small number of both descriptive and case-control studies have reported a significantly increased standardised mortality rate in female patients, which may be attributable to a lower background rate of death in the female non-SUDEP control group^{6,25}.

Epilepsy characteristics

A number of case-control studies have suggested that early onset of epilepsy is a significant risk factor for SUDEP^{21,24,26,27}. For example, an eight-fold higher SUDEP risk in patients with an onset of epilepsy between the ages of 0 and 15 years has been reported, when compared to patients with seizure onset after 45 years of age²¹ and this appears to have a male predilection¹³². However, while this may reflect a different aetiological basis for the epilepsy, it may also merely be a surrogate marker for an increased cumulative lifetime risk of having seizures for a longer period of time, as suggested by other studies^{14,19,20}. Conversely, there are several reports of a shorter duration of epilepsy being associated with an increased risk of SUDEP although this is most likely as a result of comparison with an older control population^{23,24,26}. Furthermore, following conditional multiple logistic regression analysis, a long duration of epilepsy (>30 years) was no longer a risk factor after adjustment for seizure frequency²⁸.

One would expect epilepsy syndrome to be a key factor in defining the risk of SUDEP. Yet there is only limited evidence to support the association of epilepsy syndrome with an increased risk of SUDEP^{21,27}. Discordant results from the relatively few case-control studies that assessed this risk factor and low numbers of patients in each group preclude detailed evaluation or definitive conclusions²⁵. In one study, 7 out of 57 (12%) SUDEP cases had primarily generalised epilepsy compared to 12 out of 171 (7%) control subjects. Statistical comparison revealed that there was a higher risk of SUDEP in patients with primary generalised epilepsy compared to patients with focal, symptomatic epilepsy, although this was only significant in men²¹. Nevertheless, although idiopathic primary generalised epilepsy (IGE) is usually less refractory to treatment, individuals with IGE are well represented in SUDEP cohorts. It is possible that specific epilepsy syndrome subtypes carry an increased risk of sudden death due to phenotypic expression in other cerebral and possibly cardiac structures.

Less controversy exists as to whether high seizure frequency is an independent risk factor for SUDEP. Several descriptive and large case-control studies have reported an increased risk of SUDEP in patients experiencing frequent seizures^{19,21,22,24,28,29}. This increased risk is most marked for convulsive seizures^{6-8,18,19,22,28} rather than non-convulsive episodes, such as complex partial seizures²⁴. Moreover, on logistic regression analysis, it was noted that only the frequency of

convulsive seizures was relevant, and not the frequency of all seizures combined²⁸. Conversely, high seizure frequency was not an independent risk factor in a number of other reports although a number of methodological issues exist^{8,20,25,27}. For example, in a retrospective case-control study of 42 patients with SUDEP there was no reported difference in seizure frequency between the SUDEP and non-SUDEP control groups. The study was undertaken at a tertiary referral centre, with both groups having chronic refractory epilepsy and frequent seizures²⁷. Other negative studies may have been similarly influenced²⁵. Intuitively, the *severity* of convulsive seizures may also be important in SUDEP, but this is more challenging to quantify and hence has not been evaluated as a risk factor.

Antiepileptic medication

The number of antiepileptic drugs (AEDs) taken concomitantly has been reported to be an independent risk factor for SUDEP²⁹, even after correction for seizure frequency^{21,28}. This is not universally reported however^{8,14,25-27}, although small numbers of patients and a high frequency of polytherapy in control subjects may be contributory in these negative studies. It has been shown that the risk of SUDEP increases with the number of AEDs previously taken despite correction for seizure frequency, perhaps a surrogate for epilepsy severity. Risk of SUDEP is also increased in those whose treatment history was unclear, which may reflect the risk associated with the lack of treatment and uncontrolled seizures, although the reason for this was not objectively assessed²².

Despite several descriptive studies suggesting that subtherapeutic levels of AEDs are a risk factor for SUDEP^{6,7,16,20}, this has not been corroborated by the majority of case-control studies^{25,31,32}, most likely because this is difficult to study as an independent factor. Of note is that postmortem levels of AEDs may not accurately reflect antemortem levels possibly due to, for example, redistribution and continuing metabolism³³. Compliance with AED treatment was proposed as a risk factor for SUDEP in an uncontrolled study which found 'subtherapeutic' AED levels in 68% of SUDEP cases¹⁶. Therapeutic drug monitoring has traditionally been considered a surrogate for medication adherence although, due to the existence of a number of confounding factors, it is clear that the two terms are not interchangeable. For example, in patients with uncontrolled seizures, changes of dose and type of medication are commonplace and serum levels will not be stable and may frequently be sub-therapeutic despite excellent compliance. The issue of variability of AED use was recently addressed in a study comparing hair AED concentration variability in patients with SUDEP, non-SUDEP epilepsy-related deaths, epilepsy outpatients and epilepsy inpatients. The SUDEP group showed greater hair AED concentration variability than either the outpatient or the inpatient groups, reflecting variable AED ingestion over time. However, this cannot distinguish prescribed changes from poor compliance, or identify consistent non-compliance over time. Secondly, it does not provide information on drug taking behaviour immediately before death as it takes about five days for drug sequestered into the follicle to appear at the scalp; therefore short-term non-compliance immediately before death is not assessed by this study and may have been overlooked³⁴.

Despite a number of descriptive and controlled studies, no specific AED has been clearly associated with an increased risk of SUDEP^{14,20,23,27,28,31,35}, although a small number of studies have implicated treatment with carbamazepine as an independent risk factor^{22,36,37}. For antiepileptic medication in general, proposed mechanisms include perturbed heart rate variability, lengthening of the Q-T interval on the electrocardiogram combined with a mild pro-arrhythmic effect of epileptic seizure discharges, or excessive post-seizure brainstem inhibition producing a blunting or transient abolition of the central hypoxic and hypercarbic respiratory drive, with consequent post-ictal respiratory arrest³⁶⁻³⁸. Elevated serum levels of carbamazepine have been associated with an increased risk of SUDEP even after adjustments for seizure frequency have been made. Frequent drug changes and multiple concomitant AEDs, conventional markers of severe and unstable epilepsy, increased this risk synergistically³². On this basis, it is difficult to know whether a high carbamazepine level is an independent risk factor or is merely representative of challenging epilepsy.

Perimortem features

There is evidence from both descriptive and controlled studies that a terminal convulsive seizure^{7,10,16,18,20,25,27,39}, being found alone in bed^{10,17-19,25,27} and in the prone position^{20,27} are independent risk factors for SUDEP. Whereas a small number of descriptive studies have not found an association, all case-control studies that have evaluated these factors have found a positive relationship with the risk of SUDEP. In a published report of interviews with bereaved relatives, evidence for a terminal seizure was found in 24 out of 26 cases but it is of interest that only two were witnessed. The observation that, in most studies, unwitnessed cases far outnumber those witnessed suggests that enhanced surveillance of patients with epilepsy may be protective¹⁸. This is corroborated by a study of young patients with epilepsy at a special residential school. All sudden deaths during the period of the study occurred when the pupils were not under the close supervision of the school and most were unwitnessed¹¹. Similar findings of a protective effect of enhanced supervision at night were also found in a large controlled study, where supervision was defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions, such as checks throughout the night or the use of a listening device²².

In some cases where a prone position was not observed, other factors which might compromise breathing were identified. For example, in one study only five out of 26 people were found face down in the pillow, and a sixth with the head in carpet pile. In total however, there were 11 out of 26 cases in which an extrinsic or intrinsic positional obstruction to breathing amenable to intervention may have contributed¹⁸. Moreover, it is possible that this may be an underestimate as obstructive apnoea can occur in an apparently benign position⁴⁰.

Other features

There is limited evidence for an independent relationship between learning disability and an increased risk of SUDEP. Early descriptive and population-based studies, in which learning disability was determined by observer impressions rather than by formal IQ examination, provided only weak support for this association^{7,41}. Most recent studies have found no clear correlation^{18,25-27,30} although others have reported an IQ of less than 70 to be a risk factor for SUDEP, even after accounting for seizure frequency²⁸. It has been postulated that patients with learning disability are more susceptible to central apnoea and positional asphyxia that may cause SUDEP as a result of prolonged post-ictal encephalopathy⁴², decreased post-ictal respiratory drive and impaired movement and righting reflexes²⁸. Despite early reports of an increased incidence of structural lesions in patients with SUDEP^{7,16,43}, this has not been confirmed by more recent, controlled studies^{21,27,28}. While there is evidence that psychotropic medication can influence the risk of sudden death in general, there is no convincing evidence of this being particularly relevant in SUDEP. A recent nationwide population-based cohort study of the incidence of SUDEP suggested a 5 fold higher risk of SUDEP in women with psychiatric co-morbidities than those without, and the cause of this remains uncertain¹³².

Pathophysiology of SUDEP

Pathophysiological mechanisms of SUDEP are likely to be heterogeneous and may be multifactorial. Theories propounded have focused on autonomic disturbance - particularly cardiac arrhythmias and central and obstructive apnoea and neurogenic pulmonary oedema. Additionally, the possibility of structural or functional cardiac pathology predisposing patients with epilepsy to cardiac events has been proposed.

Cerebrogenic autonomic control

The components of the central autonomic network involved in the functional relationships between cortical, subcortical and somatic regions have been elucidated from experimental and human stimulation and lesional studies. For example, it has been demonstrated that limbic structures, especially the amygdala and pyriform cortex, modulate hypothalamic function, and stimulation

of these foci can elicit both sympathetic and parasympathetic visceromotor autonomic responses⁴⁴.

Other than visual inspection of a standard 12-lead ECG, more sophisticated methods to interrogate the cardiac autonomic system have been developed, for example, measures of heart rate variability (HRV). In its simplest form this is measured in a time domain analysis as the standard deviation of R-R wave intervals^{45,46}. Frequency domain analysis permits the calculation of high-frequency (HF) and low-frequency (LF) components which assess the relative contribution of parasympathetic and sympathetic autonomic activity⁴⁷.

Cardiac mechanisms

Structural cardiac pathology. The exclusion of cardiac pathology as a contributing factor in SUDEP is challenging due to the presence of, for example, subtle abnormalities that only a detailed microscopic examination of cardiac tissue can elucidate, such as conducting system fibrosis or cardiomyopathy⁴⁸, tissue decomposition precluding the acquisition of suitable material for evaluation, lack of an appropriate control group for comparison, and the possibility of a functional rather than a structural disorder, such as ion channelopathies or pre-excitation syndromes, with normal macroscopic and microscopic examinations being implicated⁴⁹.

Increased cardiac weight has been observed in male SUDEP cases compared to control subjects⁷ although more recent studies, using more convincing methodology, have failed to replicate this earlier finding and cardiac weight is not considered to differ between SUDEP and non-SUDEP cases⁵⁰⁻⁵². Minor, non-specific pathological changes presumed to be non-fatal, such as atherosclerosis, conducting system fibrosis and diffuse myocardial fibrosis have been identified in SUDEP cases^{27,51,53,131}. It has been postulated that neurogenic coronary vasospasm may be implicated, and that if recurrent, this may eventually progress to perivascular and interstitial fibrosis⁵⁴. This may, in turn, predispose the heart to arrhythmogenesis, particularly in the setting of considerable autonomic imbalance during seizures^{55,56}. The occurrence and significance of these pathological changes in SUDEP is not universally agreed however^{50,57} and the full characterisation of the relationship between myocardial pathology and acute and recurrent seizures remains unclear at the present time.

Inter-ictal. At the simplest level, inter-ictal cardiac function can be evaluated by visually assessing a standard 12-lead ECG, primarily for evidence of conduction abnormalities, although these are frequently normal⁵⁸⁻⁶⁰ or show only minor, non-significant changes⁶¹. However, a recent preliminary study of 128 patients with severe refractory epilepsy and learning disability revealed inter-ictal ECG abnormalities in approximately 60% of patients, including first-degree atrio-ventricular block and poor R-wave progression⁶².

Early experimental studies demonstrated that inter-ictal epileptiform activity was associated with sympathetic and parasympathetic autonomic dysfunction, in a time-locked synchronised pattern^{63,64}. In the first clinical reports, analysis of inter-ictal heart rate variability in 19 patients with refractory temporal lobe epilepsy revealed frequent, high-amplitude fluctuations in heart rate which were most pronounced in poor surgical candidates⁶⁵. More recently, reduced sympathetic tone, demonstrated by decreased low-frequency power, has been seen in both focal and, albeit less markedly, primary generalised epilepsy^{45,60,65,66}. Overall, there is some evidence for inter-ictal cardiac autonomic dysfunction in patients with both focal and generalised epilepsy, possibly modulated by antiepileptic medication, in particular carbamazepine. There are conflicting reports in the literature however, suggesting that the relationship between inter-ictal epileptiform activity, antiepileptic medication and autonomic function has not yet been fully characterised.

Ictal. Arrhythmias, conduction block and repolarisation ECG abnormalities, such as atrial fibrillation, marked sinus arrhythmia, supraventricular tachycardia, atrial and ventricular premature depolarisation, bundle-branch block, high-grade atrioventricular conduction block, ST segment depression and T wave inversion have been reported in up to 56% of seizures. Abnormalities

appear to be more common in nocturnal, prolonged and generalised seizures than in focal seizures or those occurring during wakefulness^{44,67-70}.

Sinus rate change is the most common cardiac accompaniment to ictal discharge. Sinus tachycardia has been reported in 50-100% of seizures, and is dependent on the definition used and population studied^{58-60,70-76}. Although the heart rate in ictal tachycardia is typically 100-120 beats per minute⁵⁸, there are reports of rates exceeding 170 beats per minute, even during simple partial seizures^{59,71}. Ictal tachycardia is most commonly seen in the early ictal phase, soon after seizure onset^{71,73,75,76}, or rarely before clear evidence of electroclinical onset⁷⁰. This contrasts with ictal bradycardia which is seen during the late ictal phase or in the immediate post-ictal period^{77,78}. There is some evidence for right-sided lateralisation and temporal lobe localisation in patients with ictal tachycardia^{72,73,76}, corroborating the reports of early experimental and clinical stimulation studies^{79,80,81}, although it is important to note that most temporal lobe seizures are associated with ictal tachycardia, irrespective of lateralisation. In contrast, in patients with unilateral temporal lobe epilepsy being evaluated with extensive intracranial EEG electrodes, irrespective of lateralisation of ictal onset, heart rate was seen to increase incrementally as new cortical regions anywhere in the brain were recruited⁸².

Although ictal tachycardia is almost universally observed, ictal bradycardia has received more attention due to the potential progression to cardiac asystole and intuitive but unproven association with SUDEP.

The first report of ictal asystole was by Russell in 1906, who noted the disappearance of a young male patient's pulse during a seizure⁸³. The published literature since that time is, unsurprisingly, mostly case reports or small series studies, which significantly limit the number and confidence of any conclusions extracted from the data. Ictal bradycardia is observed in <5% of recorded seizures^{59,73,75,84}, but may occur in a higher percentage of patients, because a consistent cardiac response to each apparently electroclinically identical seizure is not seen⁵⁹.

A recent literature review revealed that of 65 cases of ictal bradycardia with sufficient EEG and ECG data, seizure onset was localised to the temporal lobe in 55%, the frontal lobe in 20%, the frontotemporal region in 23%, and the occipital lobe in 2%. Information regarding seizure-onset lateralisation was available in 56 cases. Seizure onset was lateralised to the left hemisphere in 63%, the right in 34%, and bilaterally in 4%. Interestingly, of 22 cases with EEG data available at the onset of the bradycardia, 12 showed bilateral hemispheric ictal activity, while six showed left-sided, and four showed right-sided activity⁷⁸. No control group data is available however. Nevertheless, it appears that there is a trend towards the left temporal lobe being implicated in ictal bradycardia, however this is not sufficiently specific to be valuable localising semiological information^{78,84}.

Ictal asystole, lasting between 4 and 60 seconds, is reported, albeit rarely, in patients with refractory epilepsy^{40,59,70,85-87}. In addition, experimental data suggests that ictal bradyarrhythmias can lead to complete heart block⁶⁴. Short periods of EEG/ECG monitoring may underestimate the prevalence of ictal asystole. For example, evaluation of a database of 6825 patients undergoing inpatient video-EEG monitoring found ictal asystole in only 0.27% of all patients with epilepsy. In contrast, a study reported on 19 patients with refractory focal epilepsy who were implanted with an ECG loop recorder for up to 18 months. Over 220,000 patient hours of ECG recording were monitored, during which time 3377 seizures (1897 complex partial or secondarily generalised tonic-clonic seizures and 1480 simple partial seizures) were reported by patients. Cardiac rhythm was captured on the implantable loop recorders in 377 seizures. Ictal bradycardia was seen in 0.24% of all seizures over the study period, and 2.1% of the recorded seizures. Seven of the 19 patients experienced ictal bradycardia. Four of these had severe bradycardia or periods of asystole which led to the insertion of a permanent pacemaker. Notably, only a small proportion of seizures for every patient were associated with significant cardiac events despite identical seizure characteristics⁵⁹.

Extrapolation of ictal bradyarrhythmias to a mechanistic explanation for SUDEP remains elusive. This is, at least partly, due to a lack of clinical evidence of common factors shared by patients with ictal bradyarrhythmias and SUDEP and the difficulty in ascertaining the importance of ictal bradyarrhythmias in SUDEP in relation to other proposed mechanisms, including other intrinsic cardiac abnormalities or apnoea and hypoxia which may aggravate arrhythmias.

Respiratory mechanisms

It is likely that primary respiratory dysfunction is involved in an important proportion of SUDEP^{40,88-94}. Alterations in respiration such as coughing, sighing, hyperventilation, irregular breathing, apnoea, increased bronchial secretions, laryngospasm, respiratory arrest, and neurogenic pulmonary oedema have all been described with seizures^{40,92,94-96}. Some form of respiratory compromise is commonly reported in witnessed cases of SUDEP⁹⁷. Electrical stimulation of multiple brain areas, particularly in limbic and temporal regions, has been demonstrated to influence respiratory activity^{98,99}, supporting the potential for seizures arising from or involving these brain regions to alter respiratory function. Central apnoea can occur secondary to the ictal discharge, acting at either the cortical or medullary level or possibly as a result of secondary endogenous opioid release influencing the brainstem respiratory nuclei directly. During post-ictal impairment of consciousness, hypercapnia and hypoxia may be less potent respiratory stimuli.

The MORTEMUS study reported on a comprehensive evaluation of cardiorespiratory arrests encountered in epilepsy monitoring units worldwide. An expert panel reviewed data, including video electroencephalogram (VEEG) and electrocardiogram material at the time of cardiorespiratory arrests. 29 cardiorespiratory arrests, including 16 SUDEP (14 at night), nine near SUDEP, and four deaths from other causes, were reported. Cardiorespiratory data, available for ten cases of SUDEP, showed a consistent and previously unrecognised pattern whereby rapid breathing (18-50 breaths per min) developed after secondary generalised tonic-clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. Where transient, this dysfunction later recurred with terminal apnoea occurring within 11 min of the end of the seizure, followed by cardiac arrest. It was concluded that SUDEP in epilepsy monitoring units primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalised tonic-clonic seizure, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnoea then cardiac arrest¹³⁶.

In a study of 17 patients with epilepsy who underwent polysomnography with cardiorespiratory monitoring in a supervised environment, ictal apnoea of greater than 10 seconds in duration was demonstrated in 20 out of 47 seizures. Oxyhaemoglobin saturation decreased to less than 85% in 10 seizures. Central apnoea, which may evolve during a focal or generalised seizure, was seen more frequently than obstructive apnoea, however the study was in a controlled environment and assistance may have minimised the likelihood of obstructive apnoea being observed⁴⁰. Larger series have since expanded the descriptions of hypoxaemia accompanying seizures¹⁰⁰⁻¹⁰². Oxygen desaturations <90% are common, occurring in approximately one-third of generalised and non-convulsive seizures¹⁰⁰. Significant desaturations have also been noted in limited electrographic seizures without clear clinical accompaniments¹⁰³. In a small number of cases (<5%), these desaturations may be profound, with measured oxygen saturation (SaO₂) <70%¹⁰⁰. Interestingly, transient bradycardia or sinus arrest has been seen in association with ictal apnoea suggesting that the reported seizure-related arrhythmias may be consecutive to ictal apnoea⁴⁰. Additional reports of ictal apnoea are typically case studies recorded incidentally during video-EEG telemetry⁹⁰⁻⁹². In a study of 135 SUDEP cases, 15 of which were witnessed, observers described respiratory difficulties, such as apnoea and obvious respiratory obstruction, in 12 patients, although the conclusions that may be drawn are significantly limited by the quality of the retrieved information and lack of additional relevant cardiorespiratory parameters⁹³. Witnesses have reported a delay between the seizure and time of death which is more consistent with primary respiratory inhibition followed by respiratory arrest and the development of hypoxia and pulmonary oedema, than 'primary'

ictal cardiac asystole²⁰. Peri-ictal hypoxaemia has been associated with male gender, younger age in children, symptomatic generalised epilepsy, temporal onset seizures, seizure lateralisation (right in adults; left in children), seizure duration, contralateral electrographic seizure spread, AED polytherapy and MRI-negative epilepsy¹⁰⁰⁻¹⁰². In a patient experiencing a seizure with oxygen desaturation, the probability of recurrence with subsequent seizures is 0.43¹⁰⁰.

Neurogenic pulmonary oedema, which may in itself be insufficient to be fatal, has been implicated in theories regarding respiratory dysfunction and SUDEP following a number of postmortem reports and case studies^{7,20,89,96}. In a sheep model of ictal sudden death, animals that died had a greater increase in pulmonary vascular pressure and hypoventilation. When airway obstruction was excluded by tracheostomy, central apnoea and hypoventilation were observed in all, causing or contributing to death in two, whereas a third animal developed heart failure with significant pathologic cardiac ischaemic changes^{88,104}. The apparent protective effect of supervision favours an important primary role for respiratory factors²², as these can be influenced by relatively unskilled intervention, such as airway protection, repositioning, or stimulation. It is unknown what proportion of SUDEP cases may be prevented by such intervention.

Suppression of cerebral activity

The possibility of progressive suppression and eventually cessation of cerebral activity as a cause of SUDEP, despite normal cardiac function, was introduced with the publication of a case report of an intracranially monitored patient who died of SUDEP in which a seizure started in one hemisphere and then spread to the other after several minutes. The EEG pattern on the original side then changed to burst-suppression with spindling spike discharges, followed by complete cessation of activity. The other hemisphere continued to show spike discharges until ceasing suddenly a few seconds later. A pulse artefact on the EEG continued for a further two minutes; there was no recording of respiratory activity. It was postulated that the loss of EEG activity was not preceded by anoxia as both hemispheres were not simultaneously affected¹⁰⁵. Post-ictal generalised EEG suppression (PGES) occurs in up to 65% or more of adult patients with convulsive seizures¹⁰⁶ and has been reported in monitored SUDEP or near SUDEP cases¹⁰⁷. PGES is more common in convulsive seizures arising from sleep¹³³. It has been shown that >50 seconds of PGES significantly increases the adjusted odds ratios for SUDEP and for each one-second increase in the duration of PGES, the odds of SUDEP increases by a factor of 1.7%¹⁰⁶. However, a small retrospective study of 17 SUDEP cases and matched controls found no significant differences in either presence or duration of PGES between the two groups¹⁰⁸ and a clear link between PGES and SUDEP continues to be elusive. A recent study evaluated sympathetic and parasympathetic changes in seizure patients by measuring electrodermal activity and heart rate variability¹⁰⁹. An increase in electrodermal activity response amplitude and a decrease in parasympathetic-modulated high-frequency power of heart rate variability were directly correlated to prolonged PGES. It is possible that PGES may serve as a marker of post-ictal autonomic dysregulation. The precise nature of the pathophysiological association is unclear. Excessive post-ictal brainstem inhibition due to seizure-induced release of GABA and other neuro-inhibitory peptides may contribute to death in some patients. This may be compounded by antiepileptic medication³⁶. This endogenous seizure-terminating mechanism could result in blunting of the central hypoxic and hypercarbic respiratory drive, resulting in post-ictal respiratory arrest, subsequent exacerbation of hypoxia, further cardiac destabilisation and death due to hypoxia and secondary cardiac arrhythmia. This is consistent with the observation that SUDEP occurs after a seizure, and could be a consequence of failed re-establishment of respiration in the post-ictal phase. It has been shown that patients with PGES are significantly more likely to be motionless in the post-ictal period and to have simple resuscitative interventions performed (suction, oxygen administration, placed in recovery position, vital signs checked)¹¹⁰. PGES in such individuals may indicate deeper post-ictal coma, more delayed arousal and, at least hypothetically, a predisposition to SUDEP. One study compared secondarily generalised convulsive seizures with and without PGES, and found that oxygen desaturation duration and extent, as well as peak end-tidal CO₂ elevation, were more marked in patients with PGES but there was no evidence of

a relationship with central apnoea¹¹¹. Early nursing interventions that reduced peri-ictal hypoxaemia were also associated with shortening of PGES duration¹¹². It remains controversial whether the occurrence of PGES is associated with increased risk of SUDEP^{106,108}.

SUDEP and epilepsy surgery

There is compelling evidence that patients with poorly controlled, predominantly generalised tonic-clonic seizures are at greatest risk of SUDEP, and a seizure is frequently seen as the terminal event. Intuitively therefore, good seizure control should translate into a reduced risk of SUDEP. The mortality rates of 393 patients who underwent epilepsy surgery were evaluated. The standardised mortality ratio (SMR) for patients with recurrent seizures post-operatively was 4.69, with a SUDEP incidence of 7.5/1000 patient-years, whereas in patients who became seizure free, there was no difference in mortality rate compared with an age- and sex-matched population¹¹³. This compares with similar studies which, for example, found a SMR of 1.8 in those with a good post-operative outcome versus 7.4 in those who failed surgery¹¹⁴. Conversely, in a large, population-based epilepsy surgery cohort, there was no association between mortality rates and seizure outcomes, although there was a clear difference between patients who underwent surgery (SUDEP incidence 2.4/1000 patient-years) and those who failed pre-surgical assessment (SUDEP incidence 6.3/1000 patient-years)¹². Moreover, there has been recent interest in the tenet that there is a common factor predisposing to surgical failure and an increased risk of SUDEP so that patients who respond poorly to surgery also carry an increased risk of SUDEP and that, overall, surgery does not alter the risk of SUDEP¹¹⁵. Proposed common factors include temporal lobe epilepsy which extends beyond the temporal lobe into the insula, frontal orbital or frontal operculum region which may favour ictal arrhythmias, central apnoea and secondary generalisation. This, in turn, would increase the risk of SUDEP and the wide epileptogenic field would translate into a poor post-operative seizure outcome¹¹⁵. Mortality studies performed in patients with vagal nerve stimulators have shown that excess mortality associated with refractory epilepsy reduced as a function of duration of use. The rate of SUDEP was 5.5/1000 patient-years in the first 24 months and 1.7/1000 patient-years thereafter, possibly reflecting gradual increase in efficacy over time. Stabilisation of measures of heart rate variability post-VNS implantation¹¹⁶⁻¹¹⁸ have paralleled the improved mortality rates, although these findings are not universal^{119,120}.

Implications for management

Despite a wealth of studies reporting on proposed risk factors or mechanisms of SUDEP this has not yet been translated into targeted therapeutic interventions and a reduced incidence of SUDEP. In spite of this being a fundamental goal in the management of patients with epilepsy, there has been a paucity of studies specifically addressing preventive or therapeutic strategies¹³⁴.

Given the disturbance in cardiac autonomic control in patients with epilepsy, there has been speculation as to whether cardiotropic medication, such as beta-antagonists, may have a protective effect, although no studies have been performed in this regard⁶⁹. Experimental studies in rats with audiogenic seizures and ictal apnoea have shown that selective serotonin reuptake inhibitors have a protective effect¹²¹, although relevant confirmatory clinical studies are lacking. Of interest however, is the recent finding of neuropathological evidence of involvement of the medullary serotonergic network in sudden infant death syndrome (SIDS) cases with a significantly lower density of serotonin receptor binding sites, particularly in male SIDS cases compared to controls¹²². Whether pharmacological modulation of the brainstem serotonergic network or cardiac autonomic function results in a protective effect remains to be seen.

The implications of the observed ictal asystole in a small cohort of patients to a larger, more representative, group of epilepsy patients is unknown. If this finding is confirmed, the potential role of pacemaker insertion in preventing a proportion of SUDEP cases needs to be assessed.

Supervision of patients with epilepsy has emerged as the only clinically important protective factor, independent of seizure control. The basis for this remains unclear but may relate to body positioning and alleviation of obstructive apnoea or possibly brainstem arousal mechanism^{11,18,22,93}.

Existing techniques for monitoring apnoea in other clinical contexts suffer from limitations which make them unsuitable for SUDEP prevention. These include the size and weight of monitors, duration of real-time monitoring, difficulty of use in unsupervised conditions and, most importantly, very poor sensitivity and specificity, mostly due to signal artefacts. Oximetry, for example, suffers from artefacts and false alarms, and the delay between beginning of apnoea and detection of oxygen saturation drop causes warnings to come late.

The first clinical study of a novel wearable apnoea detection device (WADD) has been undertaken, which proved that the device works even in the presence of artefacts in healthy subjects and individuals with sleep apnoea. WADD was evaluated in 20 healthy subjects and 10 individuals who had been referred for evaluation of possible sleep apnoea. WADD had 99.2% sensitivity, and 99.6% specificity for detection of voluntary 15–30 second apnoea whereas the automatic software of the state-of-the-art FDA approved ambulatory SOMNO system (SOMNOmedics GmbH) had 37.8% sensitivity and 90.5% specificity. For spontaneous apnoea during natural sleep and considering the expert clinician scorer as the gold-standard WADD had 91% sensitivity and 99.5% specificity. In contrast the SOMNO system had 12.1% sensitivity and 99.4% specificity.

The device that has been created for epilepsy patients is smaller than the prototype used in the above study, weighing 7.5 g instead of 17 g. The device is attached to the neck with a hydrocolloid plaster of less than 5 cm diameter and can remain in place at least overnight; it can provide over 90% sensitivity and specificity for detection of potentially dangerous apnoeas¹²³.

The ideal system for monitoring a patient's movements should have a high sensitivity and specificity, be easy to operate and be unobtrusive. Several attempts have been made to develop devices in order to alert patients and carers to an ongoing seizure, but unfortunately these attempts have universally had a very low sensitivity and specificity^{124,125}. Current approaches for SUDEP prevention are primarily based on detecting rhythmic movement caused by tonic-clonic seizures, with devices that are either worn by the person or installed in the bed. The ideal device should be validated with simultaneous ictal EEG recordings. The stationary bed seizure monitors function by either detecting noises originating from the rhythmic banging on the bed during the clonic phase of a generalised tonic-clonic seizure (GTCS) or from the bed springs¹²⁴, or changes in mattress pressure during abnormal movements¹²⁵. Several products are commercially available, but few have been tested in a clinical setting, and sensitivity and specificity are disappointingly low. The wearable devices are based on accelerometry signals, either alone¹²⁶ or in combination with other modalities, such as electrodermal response, EMG or heart rate¹²⁷. A commercially available wireless wrist accelerometer sensor tested in a clinical setting detected GTCS with a high sensitivity (90%) and a low rate of false alarms (0.2/day)¹²⁸. Surface electromyography (EMG) during convulsive seizures is another way to detect ongoing epileptic seizures. The tonic phase of GTCS is characterised by a marked increase in amplitude-derived parameters and tonic seizures have a marked increase in frequency. The devices are worn on the biceps and initial studies are promising.

The NICE Guidelines in the UK and American Epilepsy Society in the US state that tailored information and discussion between the individual, family and/or carers and healthcare professional should take account of the small but definite risk of SUDEP^{129,135}. Several studies have suggested that the relatives of people who died from SUDEP wished they had known of the risk of sudden death^{18,130}. While it is not certain that knowledge of the risks of epilepsy would necessarily prevent death, some evidence suggests that observation, positioning and, where necessary, stimulation after a seizure may protect against death. It is also likely that patients who know of the risks of epilepsy might be more adherent to AED regimens and the avoidance of trigger factors, thus reducing the

frequency of seizures. In contrast, a cohort-controlled study of SUDEP from Australia concluded that as there were no clear risk factors that were modifiable by practical intervention, disclosure to the patient of the possibility of SUDEP was inappropriate¹³¹.

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CHAPTER 39

Psychosocial outcome

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Increasingly epilepsy is being viewed as a spectrum disorder that carries a high risk of co-morbidities and negative psychosocial ramifications¹. Good seizure control does not necessarily confer positive outcomes. Awareness of the potential psychosocial problems is essential for professionals working with people with epilepsy and their families. Such difficulties can have a profound impact on quality of life, mental health and also medical management. Greater recognition of the wider impact of epilepsy is also needed to enable the development and targeting of appropriate services and support.

This chapter addresses psychosocial burdens in epilepsy and focuses on topics that have had less coverage in other sections.

Education

Most children with epilepsy attend mainstream schools, although there is an elevated risk of academic problems, lower performance levels and limited uptake of tertiary education^{2,3}. In a population based study of children with active epilepsy attending Sussex schools 72 % were classified as low achievers and 42% as under-achievers. Academic delays were encountered for reading and spelling but were most marked for sentence comprehension and computational skills². Some studies have indicated children with epilepsy are often struggling academically before they are diagnosed highlighting a role for genetic and neurodevelopmental factors. Research and clinical experience demonstrates that educational progress is also affected by seizure control, drug and surgical treatments. Psychosocial variables are also potential disrupters of educational progress. These include teacher and parental expectations, misconceptions about epilepsy, high absence rates, low self-esteem, bullying and mental health problems.

Early identification of academic problems is essential to enable the implementation of specialist educational provision and screening measures have been advocated for this purpose^{4,5}. There is limited information on the quality and efficacy of remedial educational programmes for children with epilepsy. Existing studies have not found substantial gains in academic performance following targeted educational support^{2,5}. There remains an urgent need to address academic difficulties early as epidemiological studies have demonstrated an association with poorer socioeconomic status in adulthood^{6,7}.

Employment (see also Chapter 54)

Rates of unemployment and underemployment are high for people with epilepsy even within disability groups⁸⁻¹⁰. Studies have indicated lower income levels for people with epilepsy and a recent USA study found a high number of households living below the poverty threshold^{11,12}. Poor seizure control effects employment but difficulties also arise due to personal and social factors, including discrimination, stigma, passive coping styles, low self-esteem, mood disorders, cognitive difficulties and driving restrictions.

Work has many functions aside from financial rewards. It provides a way of structuring time and, more importantly it contributes to a person’s identity and feelings of self-worth. It is therefore not surprising that unemployment is associated with an increased risk of mental health problems.

Vocational rehabilitation programmes for people with epilepsy have been shown to be effective¹⁰ but unfortunately these are not widely available. Voluntary work is an option and for some people this may lead onto paid employment. People with epilepsy who are unable to find work are supported by the benefits system in the UK but in recent years pressures to reduce this budget has resulted in many people having their finances cut and having to make appeals and attend tribunals to try and get their support reinstated. Personal Independence Payments (PIP) one key benefit has been proving particularly troublesome. PIP is intended to help with the long term costs of living with chronically ill-health. There is a 50% rule that is applicable to disorders such as epilepsy where support needed is variable. It is strongly recommended that people with epilepsy seek support and guidance when completing claim forms to maximise their chances of success as the wording is critical. Useful contacts that provide support are given in Table 1.

Table 1. Organisations which can help with benefits applications.

Organisation	Help provided	Website
Advicenow	Includes a tool to help write the set request letter, and a guide on making an appeal	advicenow.org.uk/pip-tool and advicenow.org.uk/guides/how-win-pip-appeal
C-App	Free online tool to help prepare for PIP assessment.	c-app.org.uk/
Turn2us	free online benefits calculator & grants search tool.	turn2us.org.uk
Citizens Advice	Provides advice on rights & responsibilities.	citizensadvice.org.uk
DIAL-UK	run by and for disabled people.	scope.org.uk/dial
GOV.UK	information about the range of benefits available as well as forms to download	gov.uk/browse/benefits
Disability Rights UK	free factsheets on tax credits, benefits, social care & other disability-related issues for claimants and advisers.	disabilityrightsuk.org
Welfare Rights Unit	free advice & support on benefits. Some help with completing claim forms and appealing benefits decisions.	To find your local council visit gov.uk/find-your-local-council
NI DIRECT.GOV.UK	lots of information about the benefits that are available in Northern Ireland.	nidirect.gov.uk adviceni.net
Advice NI	information, advice, advocacy, representation in Northern Ireland.	adviceni.net

Family life

Marriage and long term partnerships are a key source of social support and being embedded in a secure social network has been demonstrated as a factor that promotes psychological health. Studies undertaken over the last two decades have consistently indicated lower rates of marriage in people with epilepsy, with figures cited for European and USA samples of 48%. Male gender and an early seizure onset have been associated with lower rates of marriage and this has been attributed in part to stigma surrounding the perceived employability of the anticipated breadwinner. The impact of living with seizures within a marriage has received scant attention¹³.

Psychosocial stresses can be high for a parent of a child with epilepsy. Research studies have found a lower parent-child relationship quality, higher rates of depression in mothers and problems with family functioning. Parents may be overprotective through fear of injury or death. Families may harbour misconceptions about epilepsy and may become socially isolated due to concerns about adverse public reactions. The attitudes and understanding of families should be a prominent part of epilepsy management. Provision of accurate individual specific information about epilepsy may go a long way to allay anxieties but emotional and practical support may be needed, particularly in the context of limited family and other social support for instance as may be the case for single parents¹⁴. On a more positive note, a ten year follow up study of mothers with newly diagnosed children found good seizure control was associated with comparable quality of life ratings made by mothers with healthy children¹⁵.

Little attention has been given to the possible impact on children of having a parent with epilepsy. Parents and potential parents often raise doubts about their suitability and mothers express the greatest concerns. Fears expressed include concerns regarding inheritability and the possibility that antiepileptic drugs may lead to birth defects⁷. As children grow older, parental vigilance may intensify as a watch is kept for any behaviour or physical sign that might herald the onset of epilepsy. Older children may behave over protectively toward the parent with epilepsy and this may result in a reluctance to go to school or to go out socially with their peers.

A report of a focus group of parents with epilepsy identified four ‘persistent’ feelings¹⁶:

- i. *insecurity*: a seizure may occur anytime and a child could be hurt
- ii. *inadequacy*: not being able to take on full parental responsibilities
- iii *guilt*: children being forced to take on responsibility beyond their years
- iv *disappointment*: unfulfilled expectations of the parental role

Social networks

There is strong evidence that social support affects quality of life, physical and mental health. A major source of social support is provided by families and for some people with epilepsy the social network comprises solely of family members. Usually social support networks encompass individuals and groups outside the family that provide outlets for social companionship, emotional and/or practical support. Individuals with a good social support network usually have a sense of control over their lives and better coping mechanisms for handling adversities. In studies of people with epilepsy higher levels of social support have been linked to better quality of life and psychological well-being irrespective of seizure control¹⁷ and people with lower levels of social support have been found to be those most debilitated by their seizures¹⁸.

In a survey of young adults with epilepsy more than a third reported significant levels of loneliness and limited independence¹⁹. Lack of social support and resulting feelings of loneliness increases the risk of mental health problems. It is a matter of concern that children and young people with epilepsy indicate difficulties forming friendships Many factors may underlie limited social networks including

social anxiety, parental over-protectiveness, and limited activities outside the home. Where anxiety underlies social difficulties children and young people may benefit from individual and group psychological interventions aimed at reducing social anxiety and developing social skills²⁰.

People with epilepsy may benefit from guidance and practical support to increase their social connectedness. Engaging in community based activities is one way of establishing and broadening social networks. Sport and other leisure pursuits are good social outlets and blanket bans on activities such as swimming, cycling and using gym equipment are no longer acceptable. Risk assessments of course need to be undertaken on the basis of the clinical features of a person's epilepsy and the level of supervision available. A recent report of the ILAE task force on Sports and Epilepsy emphasised the broader benefits of physical exercise that result in not only improved physical fitness but gains in self-esteem, a wider social network and long-term improvements in general health²¹.

Social media platforms offer a major way of linking up and keeping in touch with others²². Social networking sites provide a relatively easy way to develop social networks and form connections with others including people with similar epilepsy experiences. Many people with epilepsy already participate on epilepsy forums and support groups. Social networking sites increase the opportunity for positive interactions and social engagement and provide a way of obtaining emotional and practical support and for many this helps to reduce feelings of isolation.

Stigma

Stigma can be a major factor affecting the development of social support networks. Statutory discrimination against people with epilepsy has lessened, public misperceptions about epilepsy are reducing and employers' attitudes to epilepsy are improving although discrimination remains an issue¹. Perceived stigma remains a frequently cited concern that contributes to the psychosocial burden of living with epilepsy. Stigma is strongly influenced by cultural and educational factors. A review of studies on knowledge and attitudes towards epilepsy found persisting misconceptions about epilepsy that carried the potential to adversely affect social integration and employment. One study analysed tweets containing the word seizure over a seven day period and classified 41% of the tweets as derogatory²³. Few studies have explored the effectiveness of interventions that address stigma but the available evidence suggests that while knowledge about epilepsy can be enhanced this does not always translate into positive behavioural change²⁴.

Neuropsychological deficits (see also Chapter 40)

People with epilepsy have an increased risk of cognitive deficits. Longitudinal studies have demonstrated poorer cognitive outcomes in individuals with active epilepsy^{25,26}. Much attention has been focused on memory impairments but more recently disorders of social cognition have been highlighted²⁷. Cognitive difficulties will reduce the chances of academic success and reduce employment opportunities. For individuals experiencing problems, a neuropsychological assessment may help to identify cognitive difficulties and may assist in the setting of realistic employment and educational goals. Memory deficits may lead to a loss of confidence in social settings and feelings of inadequacy. Memory rehabilitation that addresses the broader impact of memory disorders may prove beneficial²⁸.

Emotional adjustment

Living with epilepsy means coping with an uncertain prognosis regarding seizure control. Epilepsy carries increased risks of mortality and morbidity. Having epilepsy may mean coping with additional hidden deficits such as language and memory problems, or with other co-morbidities.

Diagnosis and prognosis aside, individuals have to cope with ongoing seizures. For some, these may be rare, short-lived episodes, but for others, epileptic attacks may involve bizarre behaviours, distorted awareness and perception, and embarrassing aspects such as incontinence. The unpredictability of seizures may erode self confidence and self-esteem. Public misunderstandings and stigma cause additional stress.

Individuals also have to adjust to long-term drug treatment and accompanying side effects such as weight gain, acne, unwanted facial hair, irritability and cognitive disturbances. These aspects may become more stressful at certain times of development, with adolescence being a vulnerable period. Many with poorly controlled seizures have to endure successive treatment failures, and the accompanying emotional highs and lows, as hopes are raised with the introduction of a new drug only to be dashed when seizures return. Potentially as damaging psychologically is the failure of surgical treatment, particularly when this follows several years of freedom from seizures.

Anxiety and depression are over-represented in individuals with epilepsy but are under-treated. (see also Chapter 16). A recent study indicated people with epilepsy were reluctant to seek help for mental health issues²⁹. A survey of professionals identified managing the psychological and emotional effects of epilepsy as one of the greatest challenges. NICE guidelines recommend CBT to treat depression and anxiety and there are studies that support its value in epilepsy. In the UK the Improving Access to Psychological Therapies programme has resulted in an expansion in the numbers of CBT therapists available. These can be accessed via the GP and other health professionals, with most services accepting self-referrals. Studies into the effectiveness of mindfulness based interventions has yielded some positive results, however relatively little research has been undertaken³⁰.

Recommendations

Greater awareness is needed of the wider impact of epilepsy. Improved training of health professionals is indicated, as are resources for public awareness campaigns. Emotional adjustment difficulties are more likely to develop in the context of incomplete and inaccurate information. People need pertinent, individually tailored information about seizures, treatment and lifestyle. Input is needed not only at the time of diagnosis.

In 2015, a WHO resolution recognised the psychosocial burden of living with epilepsy and called for national governments to 'implement actions to improve social in addition to medical services for people with epilepsy that promote educational and occupational opportunities free from stigma and discrimination'¹.

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CHAPTER 40

Epilepsy and cognition

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Cognitive problems encompassing learning, memory, executive function, processing speed, language, perception and intelligence may precede onset of seizures and are often present at the onset of epilepsy¹.

A range of factors will influence the cognitive phenotype and outcome including the underlying aetiology of the epilepsy syndrome, number and combination of AEDs, frequency and type of seizures, interictal EEG discharges and neuropsychiatric comorbidity.

An earlier age of seizure onset is correlated with poorer cognitive function although the evidence base is compromised by methodical heterogeneity with relatively few prospective studies. Children with epilepsy have significantly higher rates of school-based interventions such as summer school and use of tutors². School based interventions may predate seizure onset. Berg *et al* reported that 25% of children with new onset idiopathic epilepsies require special education services prior to clinical seizure onset³. Similar studies in adults are lacking.

The association between specific epilepsy syndromes and cognitive comorbidities may better reflect the neural network phenotype. Benign Epilepsy with Centrotemporal Spikes (BECTS) is a syndrome with sensory and motor facial seizures with speech disturbance ± secondary generalisation with remission of seizure during adolescence in most cases⁴. The cognitive profile is broader than language areas with subtle deficits in attention and executive functioning⁵. Juvenile myoclonic epilepsy (JME) is associated with frontothalamic hyperexcitability with compromised attention and executive functioning. However, verbal and visual memory, processing speed, naming and language function are also compromised suggestive of a network model extending beyond prefrontal circuits⁶. Cognitive deficits in mesial temporal lobe epilepsy (mTLE) with underlying hippocampal pathology extend beyond memory to incorporate executive dysfunction and language difficulties⁷.

The cause of epilepsy and the associated neuropathology often dictates the cognitive phenotype. For example, periventricular nodular heterotopia is associated with both epilepsy and dyslexia. Aberrant cortical to cortical white matter integrity has been found to be correlated with poor reading fluency⁸ whilst abnormal connections between the heterotopia and overlying cortex was related to longer seizure duration⁹. In TLE, memory deficits are associated with hippocampal atrophy. However, extratemporal cortical structural abnormalities in frontal, parietal and occipital cortex are reported as well as in subcortical and cerebellar regions with cognitive deficits extending beyond memory and incorporating executive function^{10,11}.

Age related brain development and atrophy contribute to the cognitive vulnerability in epilepsy. In healthy children, grey matter volumes decline with concomitant white matter volume increases¹². However, children with epilepsy often exhibit abnormalities in brain structure at or near the time of seizure onset and an altered development trajectory early in the course of epilepsy¹³. However, it

remains uncertain as to what degree of altered brain development is causal to cognitive abnormalities and whether these changes are permanent upon remission of seizures and cessation of treatment.

Aging-related brain atrophy includes a loss of dendritic spines, accumulation of inflammatory damage¹⁴, beta amyloid and tau protein¹⁵. These age related changes are likely to increase vulnerability to seizure-induced cognitive deficits. Patients with epilepsy have a lower baseline cognitive reserve as reflected by educational attainment or occupational complexity than healthy subjects and as a consequence may reach a clinically significant threshold of impairment earlier in life^{16,17}.

Interictal spikes (IIS) usually occur close to the seizure focus and are transient, abnormal focal neural discharges seen on EEG recordings during periods between seizures. IIS are the result of synchronous, paroxysmal depolarizations of neurons producing a rapid succession of action potentials lasting 50–200 milliseconds. Transitory cognitive impairment has been observed with both focal IIS and generalised spike-and-wave complexes^{18,19}. However, the evidence for improved cognitive outcomes by suppressing IIS remains limited.

In view of the evident cognitive burden, cognitive screening should be considered a routine component of clinical care.

The management of cognitive symptoms in epilepsy includes minimising iatrogenic symptoms in relation to the AED burden and maximising seizure control in addition to treating neuropsychiatric comorbidity. There is evidence in animal models that cognitive rehabilitation such as extensive training (“overtraining”) may ameliorate cognitive impairments in some types of epilepsy. For example, in rats exposed to early life seizures, impairments in hippocampal-dependent tasks are noted in adulthood. However, if the rats are “overtrained”, they eventually perform the task as well as controls, which may be associated with increased theta or gamma oscillations²⁰.

Cognitive rehabilitation in adults including simple external aids such as diaries, calendars or computer-assisted apps along with online or face 2 face self-management programmes can be helpful, although the evidence for consistent and sustained benefit is mixed. Non-pharmacological interventions such as special education in children and cognitive rehabilitation in adults are thought to utilise the substantial neural plasticity in the CNS with connectivity being remodelled throughout life by synaptic changes and a range of other mechanisms²¹.

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CHAPTER 41

Bone health in epilepsy

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The first case reports addressing bone health in epilepsy, specifically an association between antiepileptic drug (AED) use and abnormalities in bone metabolism, were some 40 years ago^{1,2} and prevalence rates of 50% or more have been reported for clinical and sub-clinical bone disorders in patients chronically treated with antiepileptic medication (comprehensively reviewed in Petty *et al*³). Interest has since escalated, particularly over the last decade, but despite this, a US-based survey in 2001⁴ suggests that this was an area largely neglected by treating neurologists in both adult and paediatric practice. Following this, editorials and reviews have been published on a regular basis, all highlighting what was hitherto a lack of familiarity with the current literature and urgent need for evidence-based guidelines. There seems now to be little doubt that epilepsy patients are at increased risk of fractures and metabolic bone disease, to an extent that we should be at least discussing with our patients.

Recent studies also support that at least some of this risk is AED associated, and thus potentially preventable. Since September 2018, national guidance in the UK now recommends vitamin D supplementation for people with epilepsy and borderline (25–50nmol/L) vitamin D levels (<https://cks.nice.org.uk/vitamin-d-deficiency-in-adults-treatment-and-prevention#!scenario>), but many issues remain unresolved, including which of multiple mechanisms are most important, whether newer drugs offer advantages over older, how best we should identify those most at risk, and what preventive treatment should be offered. This chapter will review the currently available literature, and discuss recommendations based on this.

Definitions and assessment

The primary symptom of metabolic bone disease is an increased incidence of fracture. Both low bone mineral density (BMD) or bone mass⁵ and vitamin D deficiency⁶ are established independent risk factors for fracture.

Bone mineral density

Low BMD without fracture is usually referred to as osteopenia, whereas osteoporosis is traditionally defined as the occurrence of non-traumatic fractures, commonly of the spine, hip and wrists, in the setting of a low BMD⁷. In the healthy population BMD peaks at around 20 years of age, remains stable until age 40, and then steadily declines, more so in post-menopausal women (Figure 1).

Creative Commons <http://cnx.org/content/col11496/1.6/> There is considerable individual variability, of which 80% is due to hereditary factors including sex and ethnicity (Caucasian women have the highest incidence of osteopenia, with Afro-Americans relatively protected)⁸. Low levels of physical activity, smoking, alcohol and hormonal status (postmenopausal women, testosterone deficient men) are also known to be associated with reduced BMD.

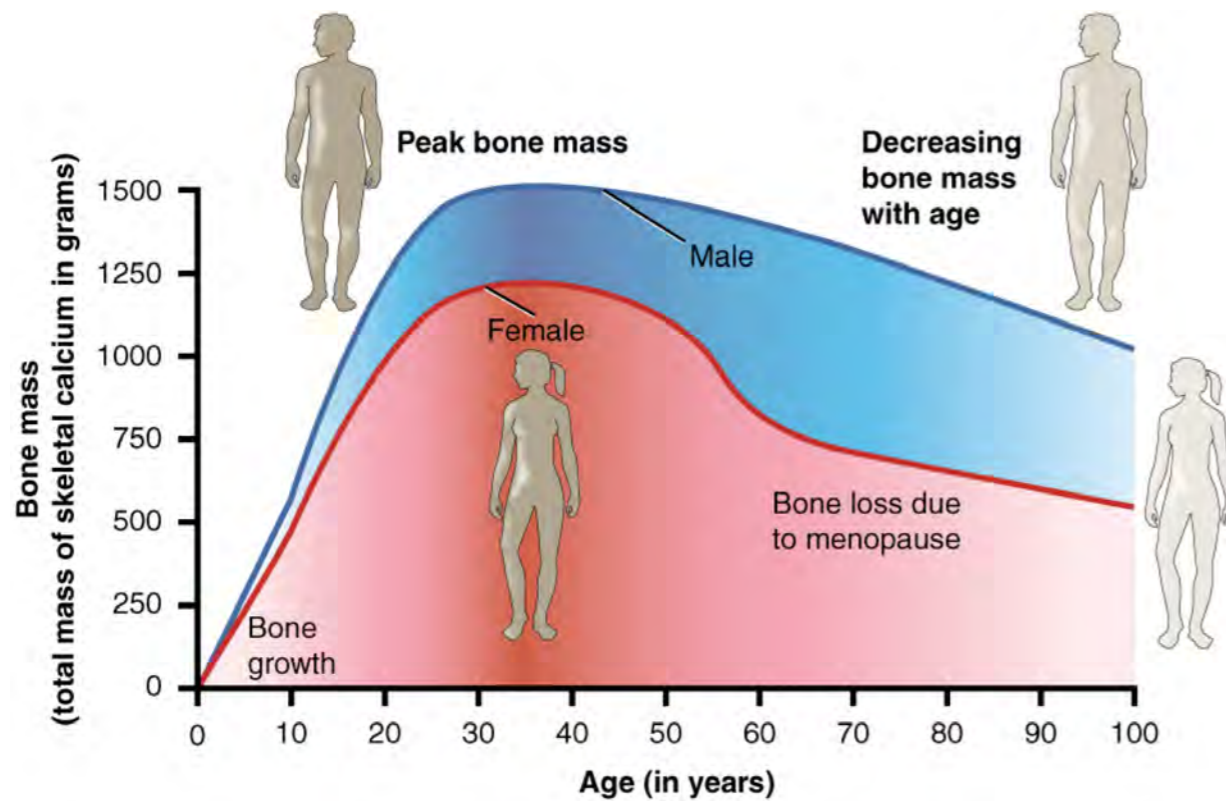


Figure 1. Bone Mineral Density with age and gender in the healthy population.

The agreed gold standard for assessing BMD is dual energy X-ray absorptiometry (DEXA), which has an accuracy of 1-2% at any given site^{9,10}. Values can be obtained for whole bones or joints, or bone cortex or trabecular bone alone. Values taken from sites of potential fracture, ideally the total hip score, are considered the most valid. The spine is not suitable for diagnostic purposes but can be used to follow treatment effects. Results are usually expressed as T scores, representing the number of standard deviations (SD) from the mean peak BMD (at age 20) for that population (sex and ethnicity).

The relationship between BMD and risk of fracture is continuous, with an approximately two-fold increase in risk with each SD decrease in BMD¹¹. The World Health Organization has defined thresholds for BMD: a T score of >-1 is regarded as normal, values between -1 and -2.5 as osteopenic, and below -2.5 as osteoporotic⁷. Osteoporosis is considered severe/established if non-traumatic fractures occur in this setting. Z scores are also sometimes quoted, particularly for children, representing the number of SDs from age-matched population controls.

Whilst relationship between BMD and fracture risk is clearly established, the use of BMD alone to assess risk is not recommended. Although it has high specificity, the sensitivity is low (approximately 50%)¹², meaning that half of fractures will occur in patients said not to have osteoporosis on this measure.

Vitamin D metabolism

The major biologically active metabolite of vitamin D is 1,25 dihydroxy vitamin D, which, in addition to its roles in bone metabolism, has antiproliferative, prodifferentiation and immunosuppressive effects. Severe vitamin D deficiency results in defective mineralisation (osteomalacia, or rickets in the developing skeleton). Serum levels of 25-hydroxy vitamin D are usually measured, and the

lower limit of normal is now 30nmol/L, but a recommendation that in individuals with other risk factors, including those on antiepileptic drugs, a level of at least 50nmol/L should be maintained.¹³

Dietary sources of vitamin D are limited, and in normal circumstances most is cutaneously synthesised, which is sunlight dependent. Thus, populations who are housebound/institutionalised, or those who avoid sunlight for cultural reasons will by default rely more on dietary sources and be at risk of deficiency. Intestinal, liver, renal or cardiopulmonary diseases are also risk factors due to secondary effects. Although frank osteomalacia/rickets is relatively rare in Western societies, vitamin D insufficiency may be very common, affecting 57% of medical inpatients in one US study¹⁴. Importantly, many of these did not have known risk factors and thus would have been missed without screening.

Biochemical markers of bone turnover

In addition to assessing vitamin D levels, and traditional biochemical bone markers such as calcium, phosphate, parathyroid hormone (PTH) and various other markers of bone turnover can easily be detected in blood and urine with commercially available kits. The bone isoform of serum alkaline phosphatase is the most commonly measured but is relatively insensitive as a screening test. There are several serum markers of bone formation including osteocalcin (a non-collagenous matrix protein secreted by osteoblasts) and circulating peptides of type I collagen. Similarly serum levels of peptides representing degraded products from osteoclastic activity (e.g. N-telopeptide of type I collagen) can be used to assess bone resorption¹⁵. Skeletal growth factors (e.g. insulin growth factor 1, IGF1) also play a role.

Bone turnover is increased during growth periods and fracture repair, and such markers have been correlated with histology from bone biopsy in both health and disease¹⁶. Such markers are often cited in papers as indicators of metabolic bone disease¹⁷, including in the epilepsy literature, but have not been validated against clinically meaningful endpoints in prospective studies. Further research is required before they can be used to detect at-risk individuals or monitor treatment, so they will not be discussed here.

Additional risks to patients with epilepsy

There are many reasons why patients with epilepsy might be at increased risk of bone disease, including reduced exposure to sunlight (housebound/institutionalised), frequent falls, and lower physical activity levels in patients with active epilepsy.

Fractures

Many of the early studies showing an increased incidence of fractures in patients with epilepsy were carried out in institutionalised patients^{18,19}, in whom low activity levels and poor sunlight exposure are important confounders. However, studies in the community and in ambulatory patients have confirmed a 2-3-fold increase in fractures in patients with epilepsy²⁰⁻²³. The most recent of these, from the UK GP database, though retrospective, was population based, and included over 40,000 epilepsy patients and 80,000 controls²³, and found the overall incidence of fractures to be doubled in epilepsy patients compared to age and sex matched controls.

This was also the conclusion from recent meta-analysis studies^{24,25}, with the highest relative risks for osteoporosis-related fractures (hip and spine), as might be predicted if metabolic bone disease is contributory. Others have reported that up to one-third of the increased risk^{21,26} appears to be a direct result of injury during seizures, again something supported by the meta-analysis²⁴ and more recent studies²⁷. Thus, optimum seizure control, especially where there are convulsive seizures and/or falls, remains a primary goal when considering bone health. Avoiding the motor complications of AED treatment that might further predispose to falls (although this has been

little studied to date^{28,29}) and being aware of general fall prevention strategies (good lighting, appropriate correction of refractive errors, etc) is also important in this context, as patients on AEDs also seem to be at higher risk of non-seizure falls than controls in at least one study²⁷.

However, the main concern is whether AEDs in themselves confer additional risks. Clearly this is important to establish, both in order to advise patients with mild/infrequent seizures and those in remission on the risks/benefits of continued AED treatment, and in terms of prevention/detection for patients continuing on AEDs. Some epidemiological studies in ambulatory patients^{21,26} found the increased risk of fractures in patients on AEDs was barely significant, once seizure-related fractures were excluded. Similarly in a recent population-based case-control study, the relative increase in fracture for patients on enzyme inducing AEDs was modest (OR 1.38, 95% CI 1.31-1.45) after adjustment for cofounders (steroids, comorbidity, social variables, prior fracture), using any fracture as outcome, and use of AEDs as exposure variable³⁰. For non-enzyme-inducers the risk was still statistically increased (OR 1.19, 95% CI 1.11-1.27), though less markedly. However, this was a huge study, totalling nearly 125,000 fractures, and a dose-response relationship could be shown for carbamazepine, phenobarbitone, oxcarbazepine and valproate, supporting that this is a biological drug effect, though not huge. Amongst individual drugs, a significant risk was not shown for any of the other newer drugs, but the authors acknowledge the study had insufficient power in this context. That any AED is associated with an increased risk, albeit higher with enzyme inducers, is supported by meta-analysis studies²⁵. Older AEDs show a clearer association, though this may reflect the inevitable bias of duration of exposure and cumulative AED load, with refractory patients often having multiple exposures, as well as the fact that more are enzyme inducers.

A large case-control study based on the UK GP database cited previously, which took account of many other confounders (though not diet and exercise), went a step further, also attempting to control for disease severity (using number of drugs/medical contacts as surrogate markers) and has shown a clear cumulative association with duration of AED use, each year of exposure being associated with a 9% increase in fracture risk³¹. This translates into up to an additional 48 fractures for every 10,000 women treated with enzyme inducers for one year, including 10 hip fractures, and four additional hip fractures in every 10,000 men³². Thus, it does appear that at least the older AEDs, including all enzyme inducers and valproate, are themselves associated with a modest increase in risk of fractures, and evidence is accumulating to support cause and effect. There is insufficient data to draw conclusions with respect to any of the newer AEDs, though there is some evidence to suggest that enzyme inducers carry a higher risk.

Biochemical markers

Prior to the last twenty years or so, nearly all published data had been in the form of case reports, cross-sectional, or retrospective studies, and thus subject to potential biases. Nonetheless there were some consistent findings.

Enzyme inducers, such as carbamazepine (CBZ), phenytoin (PHT), topiramate (TOP) and phenobarbitone (PB), would be expected to increase hepatic vitamin D catabolism, increasing the risk of osteomalacia. This may be exacerbated by additional effects on sex hormones². Phenytoin is thought also to impair directly gastrointestinal calcium absorption³³. There are now many studies (only the most recent of which are cited here as examples), including in ambulatory children and adults, consistently demonstrating significantly increased bone alkaline phosphatase³⁴⁻³⁶ (particularly with phenytoin), reduced 25-hydroxy vitamin D₃ levels^{34,37,38}, reduced serum calcium^{34,36}, and mildly elevated serum PTH³⁸ in patients on enzyme-inducing AEDs compared with matched controls. Of 2nd generation drugs, lamotrigine³⁶ looks to have fewer effects, though inevitably there is less long term data in high risk (older) populations. Conflicting data has been reported with oxcarbazepine^{35,39,40}, and there is insufficient data on other newer agents. Other markers of bone turnover also appear to be consistently elevated in patients on AEDs, both enzyme-inducing^{15,41,42}

and non-inducing, such as valproate (VPA)^{43,44}. However, not all studies are consistent in terms of specific markers or individual drugs, and in terms of detail there are many conflicting results.

A number of prospective studies have also now been reported, as summarised in Table 1^{15,45-46}. Many of these studies have also evaluated vitamin D status, and demonstrated that increased bone turnover appears to be independent of the presence of hypovitaminosis D. It is thought some AEDs, including CBZ and VPA, may have direct effects on osteoclast/osteoblast activity⁴⁷. Of note, perhaps unsurprisingly^{40,48}, both clinical^{49,50} and rat⁵²⁻⁵¹ studies also suggest that the ketogenic diet may also have a negative effect on bone health, with effects on calcium and phosphorus.

Taken together, AEDs, particularly though not exclusively enzyme inducers, do appear to have effects on biochemical markers of bone metabolism, offering a number of biologically plausible mechanisms that might underlie increased fracture risk. Hypovitaminosis D is considered an independent risk factor for fracture, and may have other consequences including muscle weakness and increased liability to falls⁵², and thus should reasonably be considered a 'warning' of clinically significant metabolic bone disease. It is also worryingly prevalent (40-80%) in epilepsy populations, both in the developed⁵³ and the developing world⁵⁴, and may develop very quickly (within months) of starting AEDs. However, other markers of increased bone turnover in themselves are not consistently associated with reduced BMD either in adults, or children⁴³. 'AED bone disease' should probably not be considered synonymous with osteoporosis, which is supported by histomorphometric data, albeit limited, illustrating increased bone remodelling⁵⁵ and not necessarily decreased cortical bone mass. Thus, whilst illustrating that there are changes to bone metabolism, the clinical significance of many of the biochemical findings, with the exception of hypovitaminosis D, is currently uncertain, and requires further study.

BMD

Given the limitations of biochemical markers, BMD remains the gold standard in terms of assessing fracture risk, monitoring disease and treatment effects in metabolic bone disease, and several studies, mostly cross-sectional or retrospective, have now reported on BMD in epilepsy patients. Many of the studies claiming a significant reduction in BMD with both enzyme-inducing AEDs^{60,61} and VPA^{44,62} use non-validated methods/sites and are thus difficult to interpret. However, those that use DEXA scanning at appropriate sites (spine, hip), and take adequate care to control for confounders, mostly support that AED use is independently associated with reduced BMD, at least in adults on older AEDs. One study found a significant association only for PHT⁴¹, but most show reduced BMD in adults on any of the older AEDs (PHT, PB, CBZ, VPA)^{37,38,63} in whom up to 59% are classified as osteopenic and 23% as osteoporotic by WHO definitions. However, the studies are inconsistent as to the size of any AED effect and whether or not this reduction correlates with either duration of AED therapy or specific drug classes. Given the now huge number of available drugs/drug combinations, this is perhaps not surprising. Using a surrogate marker of cumulative drug burden (the total duration of epilepsy multiplied by the number of AEDs), one cross-sectional from a tertiary population, all of whom had an established diagnosis of osteoporosis⁶⁴, did conclude that cumulative drug load was the dominant factor in predicting fracture risk, but this has yet to be evaluated in larger/more general populations.

Studies in children and adolescents are generally smaller, with an inevitably bigger spread of data reflecting various growth stages. Several well controlled earlier studies have not found any significant reduction in DEXA Z scores in children taking CBZ^{43,65-68} or lamotrigine^{69,70}. Others have found BMD reductions associated with treatment, especially polytherapy and long duration, though often without adequate controls for potential confounders⁷¹⁻⁷³. Similarly there are conflicting reports for VPA^{34,43,65-68,71,74}. Whether the more inconsistent nature of reports in children reflects purely methodological difficulties, shorter duration of AED therapy, that there is simply more spare capacity in younger bones that will be unmasked in later life, or that young skeletons are better able to tolerate metabolic challenges remains unclear.

Table 1. Prospective studies assessing bone health markers in relation to antiepileptic drug exposure.

Ref	Population	Drugs (n)	1st and 2nd time point on drug	Controlled for confounders*	BMD, site	Main biochemical findings
¹⁵	Children and adolescents, range 6-19y	CBZ (60)	0 and 2y	Exercise, Vit D	ND	turnover
³⁸	Adult men, mean 45y, range 25-54y	Any AED (81; most CBZ, PHT, or VPA)	Variable and + mean 19m (range 12-29)	Smoking, alcohol, diet, exercise, other drugs	femur 1.8%/yr	all
⁵⁶	Adults, mean 28.9 +/- 5y Mean 30.4 +/- 5.6y	VPA (50) Control (60)	Mean 6.7 +/- 4y and +6m	Alcohol, smoking, coffee, diet, exercise	lumbar and femur α duration	ND
⁴⁵	Children, mean 7.4 +/- 3.3y	CBZ or VPA (51) Control (80)	0 and >1y	Diet, exercise season	ND	most, Vit D all
⁵⁷	Children, mean 7.8 +/- 3.7y, range 3-15.5	VPA (15), CBZ(11), PB(4)	0 and 2y	BMI	lumbar	all
⁴⁶	Adults, range 18-50y	CBZ (10) VPA (15) LTG (8)	0 and 6m	BMI, diet, exercise	calcaneus	most Vit D incl Vit D, ctn incl Vit D, ctn
⁵⁸	Orchidectomised adult rats	LEV (8) Control (8)	0 and 12 weeks	-	femur	most, OPG, CTX1 all
⁴⁸	Adults, mean 31.0 +/- 13.1y	LEV (61)	0 and 14.1+/-3.4m	BMI, diet, exercise	lumbar other	all
⁵³	Adult mice	PHT (6) VPA (6) LEV (6)	0 and 4m		lumbar lumbar	most, AlkP HxP most, AlkP HxP all
⁴⁰	Adults, mean 28.2 +/- 8.4y	OXC (41)	0 and 11.6 +/-6m	BMI, diet, exercise	lumbar	most, Ca & AlkP

*All controlled for gender, body mass index and age y = years; m = months; n = number; CBZ = carbamazepine; LEV = levetiracetam; LTG = lamotrigine; PB = phenobarbital; VPA = Valproate; ND = not done; Vit = vitamin; no significant change; AlkP = alkaline phosphatase; BMD = bone mineral density; ctn = calcitonin; CTX1 = cross-linking telopeptide of type I collagen; HxP = hydroxyproline; OPG = osteoprotegerin

As for biochemical markers, prospective longitudinal studies (Table 1) offer the greatest potential. Despite the methodological limitations (most are underpowered, and/or inadequately controlled for confounders) the message is at least consistent in supporting that AEDs probably do contribute to reduced bone health, including reduced BMD, though it is notable that despite the fact that all these prospective studies included a broad range of biochemical parameters the mechanisms remain uncertain, and correlation between biochemical changes and BMD is generally absent. This may of course reflect different mechanisms with different drugs.

Attributable risk

In addition to epilepsy-based studies, prevalence data from various populations consistently report AED use as an independent risk factor for markers of bone disease: AED use is associated with increased fracture rates amongst ITU patients⁷⁵, increased hip fracture rates in Caucasian women in the community⁷⁶, and hypovitaminosis D in medical inpatients¹⁴. Thus overall, even allowing for confounders, the consistency of the message across different studies using different methodologies suggests this is a real association. What is more difficult to ascertain is how significant this is in clinical terms. In one study (men only) to include sequential scans two years apart, bone loss of an estimated 1.8% per year was attributable to AED use, and this was a more important risk factor than either smoking or alcohol³⁸.

A prospective community-based study of osteoporotic fractures in over 9000 women over 65 has recently reported on AED use and BMD (hip and calcaneus DEXA) with an average of 5.7 years between scans⁷⁷. With careful adjustment for confounders, the average rate of decline in total hip BMD increased from 0.7%/year in non-AED users (ever), to -0.87%/year in 'partial users' (AEDs at some time during the study, but not throughout), to -1.16%/year in continuous users (*P* for trend 0.015). Whilst these numbers sound small, such is the importance of BMD, this translates to a nearly 30% increase in the risk of hip fracture over five years, associated with AED use. Phenytoin looked the worst offender, but was also the most commonly used AED, and smaller changes with other AEDs in this study may have been masked by smaller numbers. As would be expected, the AED users were also different in other respects, e.g. as a group having less good general health, being thinner and more depressed. HRT and exercise also came through as protective factors, independent of AED usage. Across mixed-sex populations, sex and hormonal status almost certainly have a larger influence, and AED use has been estimated to contribute to only 5% of the total variation in BMD at the femoral neck⁶³. However, this does not mean men should be complacent: the same group⁷⁸ have also reported a community-based prospective BMD study in 4000 men over 65. As expected, all rates of decline were lower, but men taking notable non-enzyme inducing AEDs at both visits, an average of 4.6 years apart, still did have significantly greater rates of loss (0.53%/year vs 0.35%/year in non-users. Thus, as a potentially remedial iatrogenic cause the overall message should be cause for concern.

Case finding, treatment and prevention

On this background of confusing information, what then should we advise our patients, while awaiting the outcome of much needed further research? Much of the literature debate on this topic considers AED bone disease as a type of osteoporosis. As discussed above, this may not be strictly accurate, but given that BMD (as a measure of osteopenia/osteoporosis) is clearly related to fracture risk, and that we do have effective treatments to slow declining BMD, from a pragmatic/treatment point of view this is probably reasonable, at least until further information is available.

Published consensus guidelines¹² on the treatment and prevention of osteoporosis continue to argue, as they have done since the late 1990s, against primary prevention on the grounds that most osteoporotic fractures do not occur in the small groups at very high risk, but in the larger numbers at moderate risk. Thus population-wide interventions would be required for good effect.

The problem then is that, although the population attributable risk is high, absolute individual risk for most is low, and the safety, feasibility and cost of any intervention are especially crucial and, as yet, largely not established. Instead it is recommended that the major thrust of osteoporosis prevention should be directed towards selective case-finding or targeted risk assessment.

NICE (<https://www.nice.org.uk/guidance/cg146>) recommend an assessment of fracture risk is recommended for all women over 65 years, and men over 75 years, but in younger patients only if specific recognized risk factors (not including epilepsy) for osteoporosis are present. Assessment of absolute risks, e.g. of hip fracture over the next 10 years, using one of two web-based tools is the recommended first step. Both the FRAX (<http://www.shef.ac.uk/FRAX>) and the more recent Qfracture (<http://www.qfracture.org/>) have been externally validated in independent cohorts, and guide the clinician as to fracture risk and/or whether DEXA is indicated. Both are applicable only for adults (FRAX >40 years, QFracture >30), though the guidance also specifies that fracture risk should not be routinely assessed in anyone under 50, unless there are "major" risk factors. This reflects that the biggest risk factor for fracture, independent of BMD or anything else, is age. These ask for basic demographics and additional clinical information on proven risks (low body mass index; prior characteristic fracture; parental hip fracture; alcohol intake; smoking; rheumatoid arthritis, glucocorticoid treatment; other known cause secondary osteoporosis), Both include long-accepted secondary causes such as type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease management and, probably most significant in our patient population, prolonged immobility. However, only since 2012 has Qfracture⁷⁹ included 'epilepsy or taking anticonvulsants' as a selectable option, inferring that after some years of accumulating evidence⁸⁰, epilepsy and AED treatment *per se* are now recognised as secondary risks. Of note, emerging evidence, suggest antidepressants⁸¹ and antipsychotics⁸² may also with increased risks to bone health (with a similar magnitude of effect). Thus far, the studies are generally of lower quality than in epilepsy, with less definitive separation from confounders. However, given the frequency of psychiatric comorbidities in epilepsy, this is a concern, and is a variable recognized as such in Qfracture. Qfracture also has the advantage, for clinical use, in producing a helpful Cates plot⁸³ (figure 2) to facilitate shared patient decision-making.

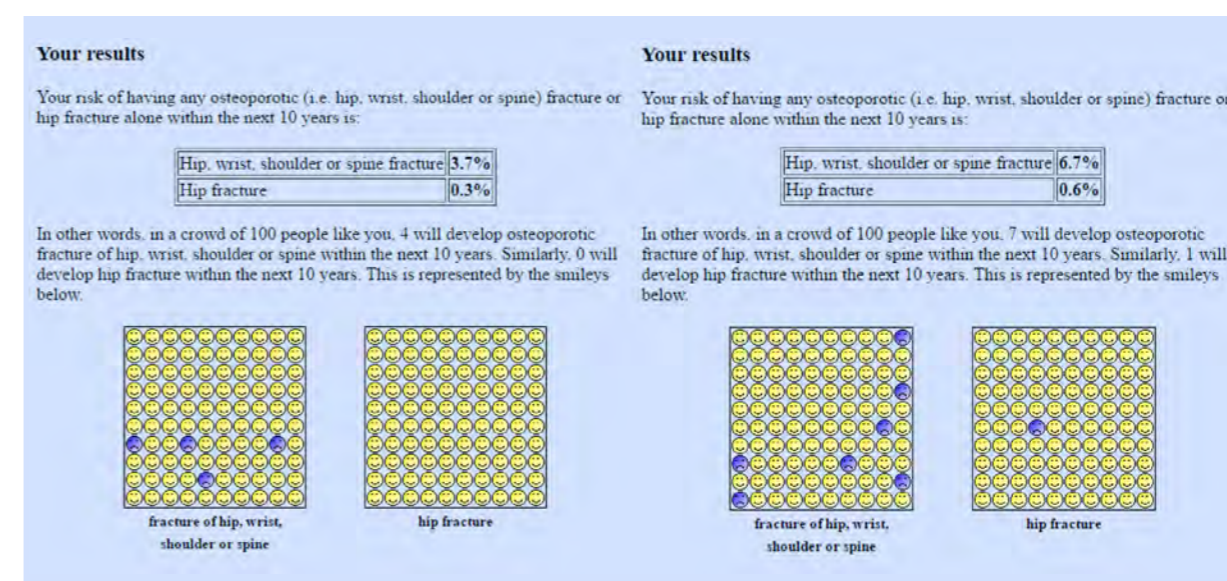


Figure 2: Illustrative output from the QFracture 2012 for a 52y woman with a positive family history for osteoporosis, no other risk factors, off (left) or on (right) antiepileptic drugs.

DEXA scanning should be used only as a case-finding strategy for individuals already considered at risk¹² using one of these tools, if the results suggest a fracture risk which might require intervention. This intervention threshold similarly changes with age, reflecting the increased absolute risk with age, as illustrated in Figure 3.

Assessment threshold - Major fracture

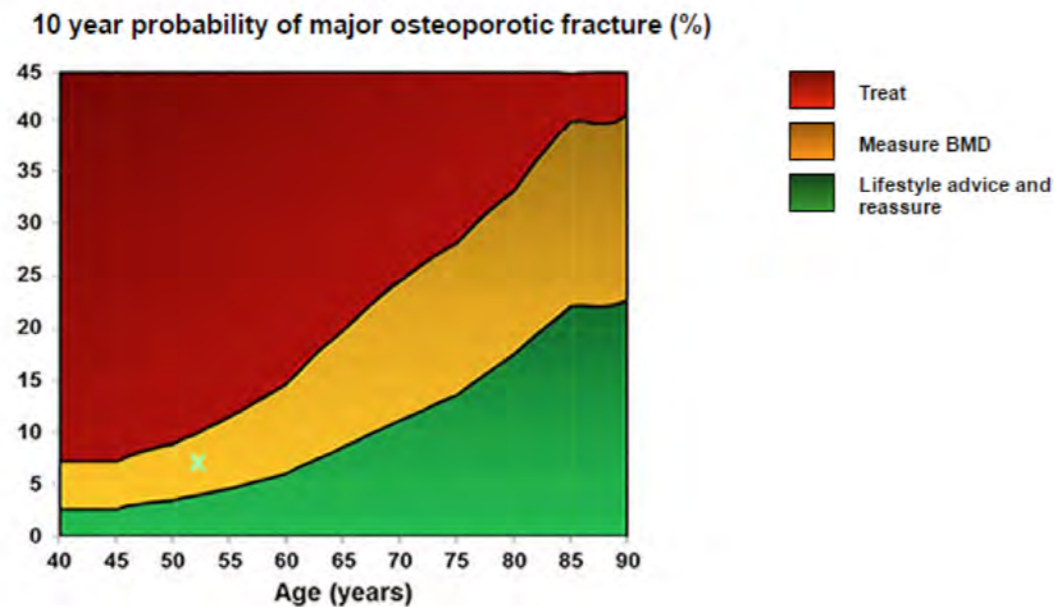


Figure 3: Output from the FRAX tool for a 52 year old woman with a positive family history, but no other risk factors. This woman should have a DEXA scan.

The bottom line is that treatment is almost never indicated unless the fracture risk is around 10% or more over 10 years, but BMD assessment may be indicated where fracture risk is approaching this in younger individuals, or 10–20% in those over 65 years. Biochemical markers are considered as having ‘the potential to aid risk assessment’ (and treatment monitoring), but their utility in clinical practice still in need of further evaluation. Thus despite recommendations from some that DEXA and biochemical markers of bone turnover should be routinely studied in patients on AEDs⁵⁵, the evidence to support anything beyond the standard bone profile every 2–5 years⁸⁴ (unchanged since 2004) is lacking.

The risk from AEDs is almost certainly substantially lower than, for example, that with steroid treatment, which is presumably why epilepsy/AEDs are still not included in what after all is an international, WHO-backed consensus guideline for osteoporosis updated as recently as 2010¹². For example, the odds ratio (OR) for fracture risk in patients on long-term glucocorticoid treatment⁸⁵ ranges from around 2 (hip) to over 5 (spine) after as little as six months’ treatment, compared to the ~1.4 OR that might be attributable to AEDs (excluding seizure-related fractures) after many years. Importantly, the cost, clinical effectiveness and service implications of including epilepsy patients as a high-risk group have also barely been evaluated, though perhaps are deserving of further research to inform future practice and guidelines.

Calcium and vitamin D supplements

The argument for ensuring adequate vitamin D levels in all patients on AEDs, notwithstanding

that there are undoubtedly vitamin D independent mechanisms³⁷, is far stronger than for DEXA scanning. As previously discussed, hypovitaminosis D appears to be a widespread problem, not just in epilepsy patients, and is an independent risk factor for fracture. Vitamin D is cheap, well tolerated, and supplementation is of proven efficacy in community-based studies of high-risk groups (principally the elderly), both with calcium¹³ and alone⁸⁶, irrespective of vitamin D status. Two randomised controlled trials of vitamin D supplementation in ambulatory children and adults on AEDs have now been reported together⁸⁷. In adults, in whom the baseline BMD was lower than in control populations consistent with other studies, after one year of supplementation only high-dose (4000 IU/day), and not low-dose (400 IU/day), vitamin D was effective as assessed by BMD increases. In children, baseline BMD was normal, but increased in both low- and high-dose treatment groups. Reflecting this, national guidance now exists recommending that vitamin D supplementation should be considered for at-risk patients taking long-term enzyme-inducing AEDs or valproate⁸⁸. ‘At risk’ and ‘long-term’ are however not defined, there is no guidance on dose or what levels to aim for in this population, and the exclusion of those on newer non-enzyme-inducing AEDs may well reflect absence of evidence, rather than evidence of safety.

Although the standard recommended daily vitamin D intake is 400 IU/day, and this is the most readily available form in combination with calcium, most published trials (not specific to epilepsy) use doses equal to 800-1100 IU/day, either daily or as a three-monthly bolus. There is also data supporting that patients on AEDs probably require higher doses, perhaps up to 4000 IU/day⁸⁹⁻⁹¹ or in some instances over 50 times the normal daily dose of vitamin D to overcome the enzyme inducing effects of phenytoin⁹², and in the epilepsy trials cited above, it was only the high dose (4000 IU in adults) which was effective. Ongoing international debate about ‘normal’ ranges, limits and recommended daily intakes further confuse the picture, with a growing expert body pushing for an increase in the acceptable lower level and recommended intakes⁹³. There is additionally no consensus on when such supplementation might be most beneficial. While a pragmatic view might be only to provide supplements to older patients most at risk, some studies have suggested that the young adult skeleton, particularly in men, is most at risk of AED-induced bone loss^{38,73}, and from the one trial in epilepsy, even low doses might be enough in children⁸⁷. Even high doses of vitamin D alone (i.e. without similarly high doses of calcium) are generally considered safe, with the minimal risk of unmasking untreated hyperparathyroidism almost certainly outweighed by the benefits. Annual costs (BNF 2010) per patient vary from £25 (standard 400 IU and calcium supplement) to £250 or more for higher doses of some formulations of vitamin D alone, many of which are less readily available and licensed only for confirmed insufficiency. For comparison, a vitamin D serum level costs around £15 to the NHS (personal communication, St George’s NHS Trust 2011), and screening has been recommended by the authors of a very balanced and comprehensive review³. Together with the suggestion that even low doses might be sufficient in children (perhaps because started earlier in their treatment history, though this has not been proven), and a recent study showing that standard supplementation from the outset can prevent otherwise rapid falls on starting AEDs⁹⁴, my own practice has shifted in recent years towards checking vitamin D status early on in treatment, and recommending a standard supplementation (calcium and 400 IU vitamin D) for those with levels between 30 to 50 nmol/L, with higher doses at least for short periods in those with levels below 30nmol/L, with a subsequent recheck. Even in a centre with a local ‘champion’, embedding in practice is difficult^{95,96}, though including a prompt on electronic prescribing has been shown to improve compliance. Ideally this should be undertaken in the context of ongoing audit/research, but this is currently precluded by resource limitations.

Treatment of identified cases

Other than ensuring adequate vitamin D, a broad range of treatment options are now available for osteoporosis including hormone replacement therapy (oestrogen in postmenopausal women, testosterone in men), bisphosphonates, recombinant PTH, oestrogen-receptor modulators,

monoclonal antibodies with effects on bone turnover, and calcitonin. No trials have been powered to detect differences in the magnitude of fracture reduction between treatments, and the vast majority have been undertaken in postmenopausal women, with little evidence in younger age groups, and also less in men, though there is no evidence that skeletal metabolism differences are fundamental between the sexes. Low-cost generic bisphosphonates which have a broad spectrum of effects are usually first line in the absence of contraindications. While previous guidelines recommended treatment of T scores below -2.5, current UK guidance requires that age, T score and the number of additional clinical risk factors (including presence of a fragility fracture or conditions 'indicative' of likely low BMD such as premature menopause, or low BMI) are taken into account. Whether and how often to perform repeat scans of patients with intermediate scores (-1 to -2.5) other than in patients on glucocorticoids (usually recommended every 1–3 years) remains controversial, and patient management should anyway be undertaken with local osteoporosis specialists. There has only been a single trial reported in patients with epilepsy⁹⁷: 80 male veterans (mean age 60 +/- 13 years) on older AEDs for at least two years (many on high-dose phenytoin) all received calcium and vitamin D supplements, and were randomised to risedronate or placebo and reassessed two years later. All of the 53 who completed the study had improved BMD, lumbar BMD significantly so, and fractures only occurred in the placebo group. However, the study was underpowered to draw conclusions.

Conclusions

There is accumulating evidence that patients on AEDs are at increased risk of metabolic bone disease and fracture for several reasons. Most of the evidence relates to the older drugs, most of which are enzyme inducers but including valproate, and there is really insufficient evidence to draw any conclusions about the safety or not of newer AEDs in the context of bone health, though levetiracetam and lamotrigine may prove preferable. That said, animal studies⁹⁸ suggest that multiple mechanisms are involved, many independent of enzyme inhibition, and that newer drugs may be equally culpable. Clinical studies supporting that this is not just an 'older' AED problem are also now beginning to emerge⁹⁹.

So, what should we do? As a minimum, in line with population guidance, clinicians should be actively thinking about bone health for patients with epilepsy and offering advice to all on regular exercise, diet, smoking and alcohol, including intake of at least 1000 mg/day of dietary calcium, and at least 400 IU/day of vitamin D. The 2018 UK Vitamin D guidance (<https://cks.nice.org.uk/vitamin-d-deficiency-in-adults-treatment-and-prevention#!scenario>), now includes a specific recommendation that whereas a serum level of at least 25nmol/L is sufficient for most, those with additional risk factors including epilepsy should aim for 50nmol/L. An inevitable conclusion is that at some point serum levels should be checked, taking into account the time of year and any supplements the patient is taking when interpreting the result. Whether it might be cost effective to suggest a standard supplement for everyone when starting AEDs at least in the UK autumn/winter, potentially reducing the proportion who might then need a higher dose at some point remains to be established. However, including vitamin D in the recommended 2–5 year 'bone profile' seems reasonable¹⁰⁰.

There is insufficient evidence to justify regarding patients with epilepsy as any different from other groups with respect to DEXA scanning and treatment, and they should thus be managed in line with population guidance in this context. This means that for patients over 40 years, clinicians should be asking about additional risk factors which might 'tip the balance' such as prior fragility fractures, other secondary causes (of which prolonged immobility is probably the most prevalent in the epilepsy population), and family history, noting those with other recognised secondary causes, and where appropriate utilising the Qfracture tool to guide further investigation and management. In terms of who should be driving this in patients with epilepsy, national guidelines put the onus

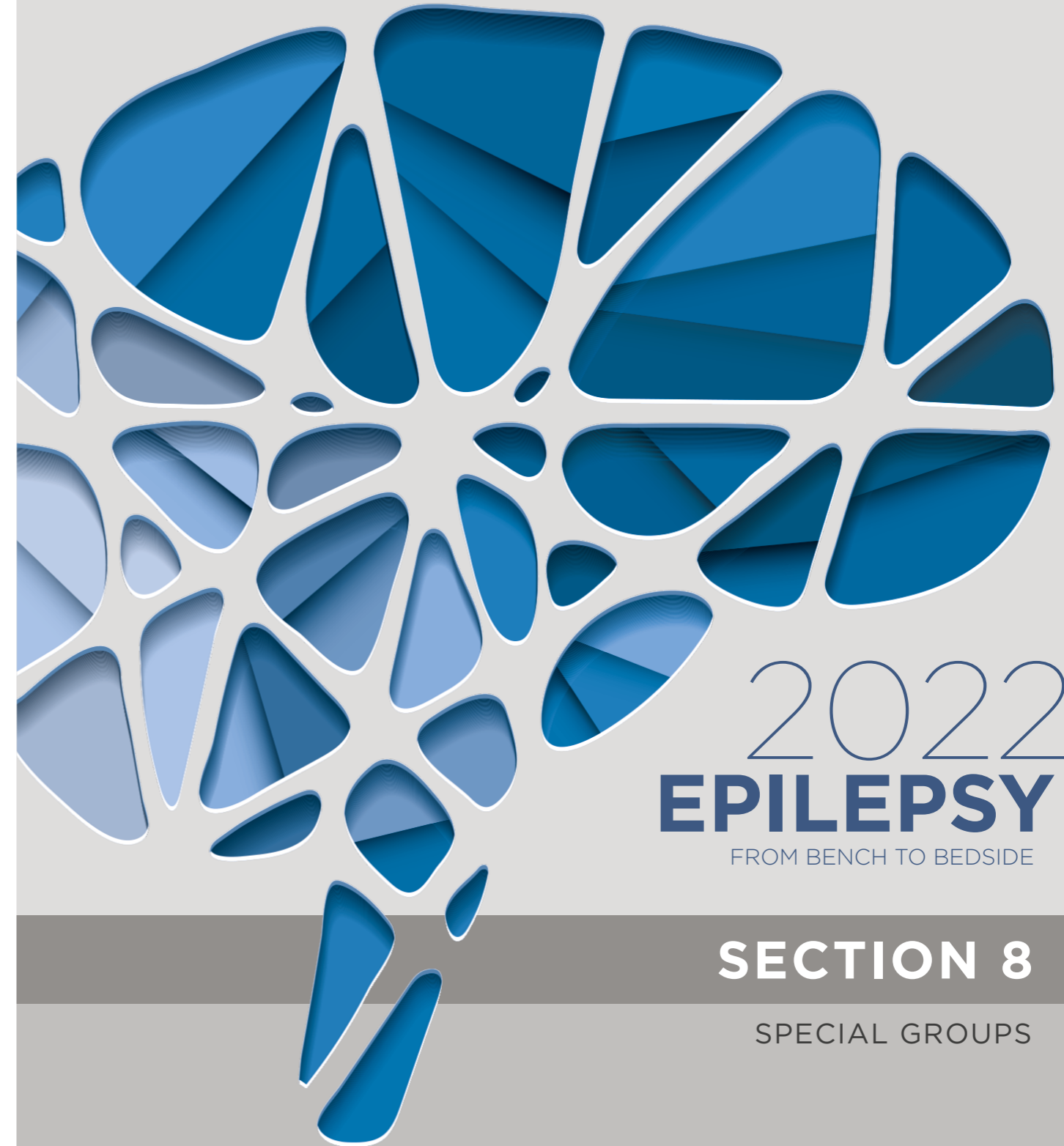
of responsibility very much in the hands of the GP to monitor the use of medications that might be associated with falls or fracture, to ensure prescription of calcium and vitamin D and to encourage adherence to therapy¹². However, it is also known that patients with epilepsy are less well informed on bone health issues than the general population¹⁰¹, with highly variable clinical practice in this area¹⁰². It is not known whether this reflects poor knowledge among those managing epilepsy, the higher prevalence of learning, memory and psychosocial problems in patients with epilepsy, or that for the general physician or indeed the specialist epileptologist managing a patient with epilepsy, bone health simply falls down the list of priorities. However, pending additional evidence on screening, prevention and treatment in relation to bone health in epilepsy, dependent on much needed further research, at least for the time being, my own view is that this is an area neurologists need to lead on, working in collaboration with GPs and local prescribing leads to better serve our patients.

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 8

SPECIAL GROUPS

CHAPTER 42

Epilepsy and intellectual disability

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Introduction

The prevalence of intellectual disability worldwide is estimated at 1%. Intellectual disability is defined as deficiencies in intellectual functioning and learning (IQ less than 70) as well as difficulties in adaptive behavior, all starting within the developmental period (before the age of 18). The severity of intellectual disability can range from mild to profound and can occur in isolation or in combination with other physical impairments or comorbidities including epilepsy¹.

Epidemiology

Epidemiological issues in 'special groups' by their nature are liable to bias and confounding, this being further complicated in the ID/epilepsy population by cohort effects arising from changing definitions and diagnostic practices over time³. These reservations acknowledged, and although incorporating many studies based on were cross sectional quasi-opportunistic surveys, retrospective review of records, self-reports or interviews, a recent systematic review concluded that in general samples of people with ID, one in five would have epilepsy.

Stratified by severity of ID, prevalence of epilepsy in moderate to profound ID is 30.4% (95% CI 25.5–35.7) as compared to 9.8% (95% CI 7.6–12.4) for mild ID. ID combined with epilepsy predicts a greater level of associated impairment².

In summary, it can be said with reasonable confidence that epilepsy affects approximately 22% of people with ID and its prevalence positively correlates with the severity of the disability. The corollary is that a quarter of people with epilepsy have an ID^{1,2}.

In comparison with the general population, epilepsy in people with ID tends to be more severe, more likely to be treatment resistant and associated with higher morbidity and mortality.

Aetiology

Aetiological factors

Intellectual disability in a substantial number of cases can be attributed to a specific brain insult in utero or early life but until relatively recently most were assumed to be idiopathic. However, technological advances are increasingly revealing these to be associated with genetic abnormalities that in some cases can be assumed to have been causative and that may in turn serve to identify specific epilepsy syndromes.

Table 1. Epidemiological surveys of the prevalence of epilepsy in people with mental and physical handicap⁴⁻⁹.

Study	Sample	Prevalence
Mariani <i>et al</i> (1993) ⁴	Institution	32%
Steffenburg <i>et al</i> (1995) ⁵	Children 6-13 year old	
	Community	
	MMR	14%
	SMR	24%
Welsh Office (1995) ⁶	Adults Community-based All MR	22.1%
Airaksinen <i>et al</i> (2000) ⁷	Children with ID born 1969-1972 Prospective cohort study Community-based All MR	21.2%
Arvio and Sillanpaa (2003) ⁸	All ages Community register Severe to profound MR	51.8%
Mathews <i>et al</i> (2008) ⁹	Adults Community (GP) Level of MR not specified	18.2%

MMR: mild mental retardation, IQ 50-70; SMR: severe mental retardation, IQ <50

As outlined below specific aetiological diagnosis may yield therapeutic insights only relative rarely, or its role be restricted to genetic counseling¹². However, the field is developing rapidly and is beginning to have a wider application than the paediatric population. In that sense, it is important to recognize that most diagnoses of ID and epilepsy were made prior to these technologies being available and that many adults have not had access to new investigations. In one retrospective study of people with intractable epilepsy and developmental delay, genetic causes were identified in 28% of cases and a treatable metabolic disease in 4,5%¹³.

Epilepsy phenotypes

Although genetic studies have substantially improved our understating of the causes of ID and pedigrees, specific genetic markers or gene products mapping onto specific epilepsy phenotypes are being identified, their overall clinical relevance is still limited. I have listed below some illustrative examples of syndromes of intellectual disability where epilepsy is an important feature, but specific learning disability syndromes associated with specific seizure semiology are still the exception rather than the rule, although some broad observations can be made and clinically relevant pointers drawn.

At the outset, it is important to note that although epilepsy is far commoner in the ID population there are a number of clinically relevant negative associations that run counter to an assumption of inevitably intractable or complex epilepsy.

Epilepsy in Down's syndrome is bimodal, being limited to the extremes of age span and relatively unusual in the interim. Infantile spasms present in infancy, generalized seizures in those over the age of 50 associated with Alzheimer's disease. Seizures associated with dementia tend to respond well to a broad-spectrum anticonvulsant¹⁶.

Fragile X syndrome is the second most common cause of intellectual disability with a prevalence of 1/4000 in males and 1/ 8000 in females. Males are more severely affected than females, with higher level of ID, and more marked dysmorphic features. Only 15% also have epilepsy, which tends to be relatively benign and improves with age¹⁴.

By contrast, in Angelman syndrome, another rare genetic disorder (1/15000) associated with profound ID, ataxic gait and movement disorder epilepsy is far more common¹⁴.

Tuberous sclerosis is an autosomal dominant disease associated with intellectual disability in 50% of the affected people, autism spectrum disorder and behavioural problems. Although relatively subtle in its associated clinical features, almost all affected people develop epilepsy often starting in the first year of life with multiple seizure types that are usually treatment resistant.

Rett's syndrome is a rare disorder affecting mostly girls and albeit associated with true epilepsy has a high potential for misdiagnosis of its associated features as epilepsy. Development is normal until the age of 6 to 18 months, at which point the affected girls develop severe communication, coordination and learning difficulties. Stereotypical repetitive hand wringing, or flapping are a characteristic, as well as breath holding or other breathing difficulties and abnormal eye movements including excessive blinking, all of which are commonly mistaken for epilepsy^{14,15}.

Lastly, two recently described and elucidated genetic disorders are Dravet syndrome and GLUT 1 deficiency. Although rare, their identification even in adults can result in new and more effective therapeutic options for the affected individuals.

Dravet syndrome is the most severe phenotype of the SCN1A mutation-related syndromes, with onset in the first year of life, often presenting with prolonged febrile or afebrile generalized clonic or hemiclonic seizures. Other seizure types develop between the ages of 1 and 4 and tend to be severe and resistant to standard antiepileptic drugs. From the age of 2, progressive cognitive behavioral and motor impairment is evident. Since this is a sodium channelopathy, these patients' seizures deteriorate if treated with sodium channel blocker anticonvulsants. There are specific drugs with good response rates, including Stiripentol and cannabidiol.

GLUT1 deficiency syndrome is associated with cognitive impairment and seizure as well as movement disorder worsened by exertion (including ataxia). Seizures start before the age of 6 months, and the severity and frequency varies between individuals. The main treatment is a ketogenic diet, which is highly effective in controlling seizures and improving movement disorder. Although early treatment results in better outcomes, adults affected can also benefit. It is also important that in patients with GLUT1 deficiency, barbiturates and sodium valproate should be avoided¹⁸.

Diagnostic challenges

Risk of misdiagnosis

In the general population the misdiagnosis of epilepsy remains an issue with reported rates as high as 25%¹⁹. Misdiagnosis is also a recognised problem amongst people with intellectual disability where, as I've tried to illustrate above, the additional complexities place this group at a high risk of both overdiagnosis and underdiagnosis. The presentation of epilepsy in people with intellectual disabilities is often atypical due to other comorbidities including; associated autism, sensory and motor impairment and stereotypical or challenging behaviour.

Although the negative implications of a misdiagnosis are potentially significant in either direction, with unnecessary treatment with antiepileptic drugs if epilepsy is wrongly diagnosed and persisting untreated seizures if it isn't, it should not be assumed that erring on the side of caution mandates treatment of epilepsy on a basis of unconfirmed suspicion¹⁵. In some patients with complex comorbidities, it is better to acknowledge uncertainty than to make a hasty and incorrect diagnosis²⁰.

Diagnosis "by proxy "

In people with learning disability, a witness report from a carer or family member is common; a report from the individual is less so. Thus, our history will commonly progress through another. The degree of this will increase as the individual's communicative skills decrease.

Having to rely on descriptions or past history given by carers contributes to the rate of misdiagnosis in patients with ID. Carers often have not been properly trained, have little knowledge of epilepsy, or do not know the patients well. One study found that most of the "new seizure" type reported by carers working in an institution were in fact non-epileptic or variations of the patient's original epileptic seizures. A systematic review has identified poor training and lack of continuity of staff as contributing to misdiagnosis of epilepsy in the care settings specific to ID but these factors also apply to health professionals in general settings¹⁵.

Paroxysmal events that can be mistaken for epileptic seizures in patients with ID.

Repetitive episodes of manneristic or stereotyped behaviour would be most unusual in many people without handicaps and the diagnosis of epilepsy would be highly likely. However, in a young man with autism, for example, such behaviors may be reflections of the cognitive disturbance of the autism and not in fact epilepsy. Clinicians need a structured approach to this differentiation, and a detailed clinical history.

The main behavioral events that can potentially be misdiagnosed as epilepsy in patients with ID include; stereotypies, sudden movements and postures, spontaneous smiling or grimacing, day dreaming, repeated blinking or swallowing, hyperventilation and rhythmic self-stimulatory behaviors or tics^{21,22}.

Physiological events that can also be mistaken for epilepsy include; dystonic posturing, ataxia with falls, clonus or head or eye turning^{21,22}.

Psychogenic seizures are not unusual in patients with mild to moderate ID. By contrast, with patients presenting with psychogenic seizures in the non-ID population, a significant number have coexisting epilepsy. The underlying cause, once identified, is generally homely and readily understandable and at least in the short to medium term readily addressed assuming a sufficient degree of understanding and assertive confidence on the part of carers once a formulation is established.

Figure 1 (found at the end of chapter) sets out guidelines for the clinician to assess the relative likelihood that behaviour is linked to epilepsy or its treatment. The key element of this assessment is the ability to describe the meaning of the behaviour, the so-called 'functional analysis of behaviour'. This may in fact need to be done with such a degree of sophistication that referral to, and working with, community

Antiepileptic drugs

People with learning disabilities account for 60% of the population with treatment resistant epilepsy and are therefore more likely to be on polypharmacy. This group is also at increased risk

of developing side effects, which can be difficult to recognise, particularly in patients with severe to profound ID and no verbal communication³⁰.

A Cochrane review on pharmacological intervention for people with ID and treatment resistant epilepsy concluded that there is evidence for the use of AEDs to reduce seizure frequency in this population. It also found that the side effect profile in patients with ID is very similar to the general population³¹.

In terms of the initiation treatment, it is good practice to start medication at low doses and titrate slowly with close monitoring of side effects. When considering starting a new drug it is important to take into account other comorbidities, drug interactions and to have a good understanding of the patient's normal baseline (not only in terms of seizure frequency but also behaviour, level of alertness and mood changes) before starting a new drug, to make sure that new side effects are correctly identified.

Patients with ID are at higher risk of being on polypharmacy and it is therefore important that if there is no evidence of efficacy after introducing a new drug for a reasonable trial period, the drug is withdrawn.

Evidence for prescribing individual AEDs in this population is poor. In terms of the older drugs, Carbamazepine remains commonly prescribed. However, its side effect profile (dizziness, nausea and drowsiness) and potential drug interactions have to be taken into consideration. There is some evidence that slow-release preparations are better tolerated in patients with ID³².

Sodium valproate is another older drug that remains first-line treatment for males with primary generalised epilepsy. There is also some evidence of its efficacy in reducing seizures in people with ID. People with ID are, however, at increased risk of developing valproate-induced hyperammonaemia encephalopathy, which may not be readily identified³².

Finally, phenytoin should be used only as a last resort due to its short and long-term side effect profile, the need for drug monitoring and potential drug interactions³³.

In terms of the newer drugs, most of the available evidence on efficacy and tolerability in patients with ID is for Lamotrigine, although this evidence is from small studies of poor quality. Lamotrigine appears to be well tolerated and efficacious. However, in a third of patients there was evidence of deterioration of seizures. Gabapentin seems to be as well tolerated as Lamotrigine^{30,32}.

There is also evidence from a double-blind placebo-controlled trial that Topiramate is efficacious, and, overall, well-tolerated³⁴.

A multicentre study of adults with refractory epilepsy prescribed Perampanel found that it is well tolerated. However, caution is advised when prescribing Perampanel for patients with mental health or behavioral problems³⁵. Another study on treatment with Brivaracetam for people with ID concluded that it seems to be effective in a small number of patients suffering from difficult-to-treat epilepsy. However, challenging behaviour was documented in a significant number of patients, with psychiatric illness being a risk factor for this^{36,37}.

Practical prescribing for people with intellectual disabilities

The clinician treating people with ID has to be aware that side effects that would be mild and easily tolerated by patients without ID can be severe and have a profound impact on patients' and carers' quality of life.

When prescribing for patient with complex needs, the clinician should consider side effects in relation to the patient's specific difficulties.

Challenging behaviour: Up to 15% of people with ID have challenging behaviour. Some AEDs can increase irritability or aggression, for example Levetiracetam and Perampanel. An increase of irritability in someone who already has behavioural difficulties would potentially turn a just-about manageable situation into a totally unmanageable one. However, behavioural toxicity is not so prevalent or predictable as to completely rule these out as options and prescription is a matter of being available to reassess the situation as necessary and being confident in what constitutes a stopping point³⁸.

Communication difficulties: one of the side effects of some anti-epileptic drugs including Topiramate is word finding difficulties, which for someone with very limited speech can result in a significant deterioration of their ability to communicate.

Problems with appetite: the effect on appetite and weight of some AEDs has also to be considered. A drug that reduces appetite like Topiramate or Zinozamide may not be a good choice for a patient with a very low BMI. Alternatively, for someone who is overweight or has challenging behaviour around food introducing a drug that increases appetite like sodium valproate or Gabapentin would exacerbate all these problems.

Sedation: most AED can be sedative particularly at higher doses. The impact of sedation in someone with cognitive difficulties can be very significant, including reducing mobility, ability to engage with activities or other people.

Mobility: dizziness and ataxia are also recognised side effects of some AEDs and for people with ID and reduced mobility or balance problems, even very mild side effects would result in a significant reduction of mobility and higher risk of falls.

Risk of osteoporosis: people with ID have increase risk factors associated with osteoporosis, in particular reduced mobility and taking anti-epileptic drugs. In general, for this population it is important to avoid enzyme-inducing anticonvulsants and minimise polypharmacy if at all possible³⁹.

Teratogenic potential: this also needs to be considered for this group of patients, in particular for female patients with mild ID.

Drug preparation:

Some patient with ID would not be able to swallow tablets. Therefore, alternative preparation like syrup, granules or soluble tablets should to be considered. Refusal of oral medication can also be an issue and medication may need to be administered covertly.

It is not uncommon for people with severe or profound ID to be on long term feeding through a PEG, which has implications for the type of drug and preparation prescribed. Broadly speaking PEG feeding has effects on absorption similar to those recognised in gastric bypass⁴⁰.

Benzodiazepines:

Benzodiazepines are regularly used to treat seizures in the context of rescue medication or as an add-on treatment. As well as potential for tolerance and sedation, some patients with ID (with or without autism) can have a paradoxical response to benzodiazepines resulting in hyperactivity and insomnia.

Clobazam is efficacious and has a good safety profile as well as being less sedative than other benzodiazepines and up to 30% of patients can take it long term without developing tolerance.

In any case, the clinician treating patients with ID should avoid high doses and closely monitor side effects, particularly sedation⁴¹.

Rescue medication:

Buccal midazolam is as effective a rectal diazepam at controlling prolonged seizures but is also easier to administer and far more acceptable to patients and carers.

For many patients with ID Midazolam is administered by professional carers. Therefore, a clear protocol and adequate training is required. There is now a Best Practice Guideline for professional carers in the UK⁴².

Non-pharmacological treatment options

The most recent Cochrane review on evidence for non-pharmacological intervention to treat epilepsy in people with ID found very few studies addressing this issue and no good quality randomised controlled trials.

Ketogenic diet

Evidence for the effectiveness of the ketogenic diet is mostly for children (with or without ID.) It can be effective for people with refractory epilepsy; however, compliance and tolerability are an issue⁴².

Epilepsy surgery

Intellectual disability is not a contraindication for epilepsy surgery. Often patients with low IQ are not considered for surgery as it is assumed that ID reflects diffuse brain damage or due to concerns of poor cognitive outcomes.

There is evidence, however, that patients with ID can benefit from curative or palliative surgical procedures. Patient with Lennox-Gastaut, for example, can have successful results after resective surgery if there is evidence of dominance of EEG abnormality in one hemisphere⁴⁴.

A review of long term outcomes following surgery in patients with ID found that low IQ was a negative predictor for seizure freedom. However, most patients benefitted from surgery due to significant seizure reduction. Children with ID have better outcomes than adults, not only in terms of seizure freedom but also in terms of improved cognition and behaviour if treatment is carried out relatively soon after onset of epilepsy^{45,46}.

Palliative surgical procedures including corpus callosotomy or insertion of a vagal nerve stimulators are also effective non-pharmacological interventions that can improve seizure control in patients with ID with intractable seizures⁴⁶.

Capacity

It is important to bear in mind that having a learning disability does not automatically make this person incapable of making decisions. Capacity is situation-specific; therefore, someone may not have the capacity to make decisions for complex interventions like epilepsy surgery but may be capable of making a decision regarding antiepileptic drug treatment. Even in the case of someone who does not have capacity it is important to make an effort to support their involvement in making decisions as far as possible.

If the person does not have capacity, the clinician also needs to know if there is a welfare attorney or guardian who has a power to consent to medical treatment and therefore must be consulted.

Table 3. Differentiating seizure and behaviour disorder.

Seizure	Behaviour disturbance
Identical behaviour on each occasion	Variation in behaviour with circumstances
No precipitant	Often associated with precipitant such as a demand, need to avoid a situation etc.
Unresponsive to communication, calming	Responsive to calming, support, removal from stressor
Investigations: Analysis of behaviour: no relationship between behaviour and environment Video: Shows typical seizure features EEG: positive inter-ictal EEG	Investigations: Analysis of behaviour: relationship found. Video: Atypical picture seen EEG: negative inter-ictal EEG of some use

Risk Assessment

People with learning disabilities have a shorter life expectancy compared with the general population and comorbid epilepsy is associated with an even higher mortality. After respiratory disease, SUDEP is the most common cause of death in this group of patients and convulsions have been identified as the main potentially preventable cause of death^{24,47}.

Practitioners working with people with a learning disability should be aware of their requirement to assess and support the range of potential risk in this patient group.

In all cases, a three-stage approach to risk assessment and management can be helpful. Firstly, identifying the precise risk. Secondly, individualizing the risk to the individual's seizure type, frequency and capacity and lastly implementing the risk reduction plan.

Models of Care

Although clearly disadvantaged within current services there is very little evidence for any particular model of care for patients with ID and epilepsy^{50,51}.

Patients with intellectual disabilities face health inequalities in general. Several surveys and audits have highlighted that this is also the case for epilepsy care in this population⁴⁸. A recent survey of epilepsy services for people with ID in Scotland found clear inconsistencies and fragmentation of care throughout the country as well as limited access to epilepsy specialists, clinical investigations and timely review. Other surveys based in England have reported very similar findings^{49,50}.

Poor communication and lack of involvement of the patients with ID in their own treatment is a frequent complaint of carers and patients. Patients value the input of learning disability and epilepsy specialist nurses, although these last remain a limited resource^{49,50}.

Conclusion

The prevalence of epilepsy in people with ID has been estimated as 20 times higher than that in the general population. Patients with ID are more likely to be drug resistant and to have severe epilepsy. Despite all of this, this group is often deprived of access to optimum health care⁵².

Due to the frequent occurrence of complex comorbidities, the risk of misdiagnosis is high and the consequences very significant for patients. Even when the diagnosis of epilepsy is accurate, clinicians' low expectations for this population mean that an aetiological diagnosis is not pursued despite their being the population, par excellence, where increasing knowledge of molecular genetics are likely to inform new treatments⁵³.

Clinicians looking after this group of patients need to be aware of all these issues and adjust their practice to take into account the particular needs of people with intellectual disabilities.

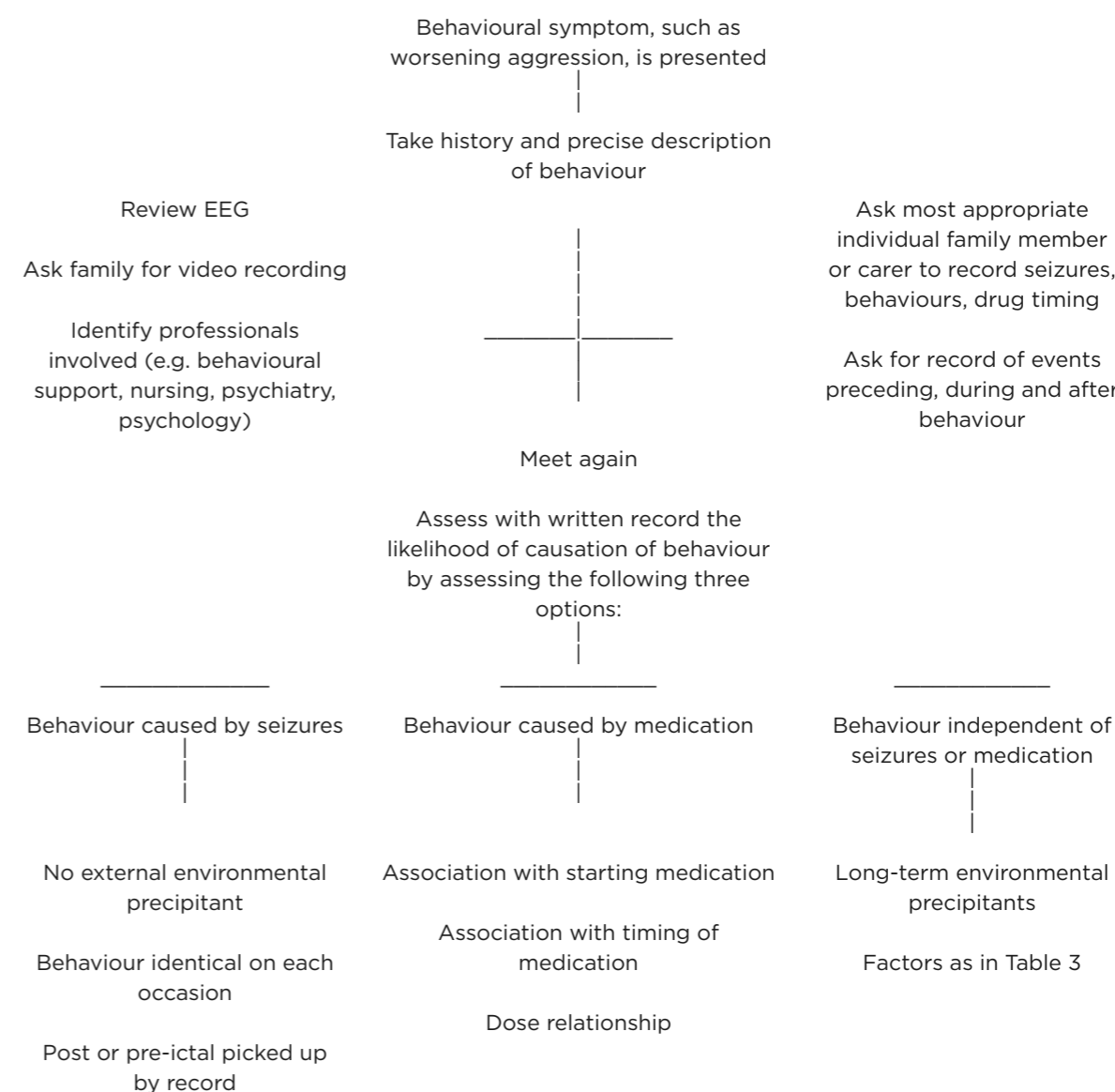


Figure 1. Assessing behavioural symptoms in epilepsy in people with learning disability.

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CHAPTER 43

Epilepsy in adolescence

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Introduction

Although the incidence of epilepsy is high in adolescence and the prevalence of psychiatric disorder is also higher than in childhood or adulthood, specific services for adolescents with epilepsy are rarely provided and this subject receives surprisingly little attention in many books on epilepsy. Adolescence is a time of great change; growth into adulthood and issues such as preparation for university or employment, driving, drinking, social/sexual relationships, marriage/conception, as well as a general increase of responsibility need to be considered. Epilepsy impinges on all these areas to a significant if not major degree. In addition, adolescents tend to be very body-conscious and do not like to be different from their peer group. The stigma associated with a condition which implies loss of control and requires the regular taking of medication is liable to have a very negative effect on the adolescent unless the situation is managed well¹. Denial of the epilepsy may result in some teenagers taking risks, such as refusing to accept medication or other precautions.

The subject of epilepsy in adolescence has been covered in a number of reviews²⁻⁶.

Management dilemmas

There are some specific management dilemmas in adolescents with epilepsy. Although the focus of both the initial interview and follow-up discussions should be on the adolescent, because the history depends so much on the account of someone who has actually seen the seizures it is generally also necessary to interview the parents. This situation needs to be explained to the adolescent.

Sodium valproate remains one of the most effective antiepileptic drugs for juvenile myoclonic epilepsy (JME). However, it may be associated with weight gain - a particularly unfortunate adverse effect in body-conscious female patients, who may refuse to continue taking the drug. There has been considerable debate in the literature about the apparent association of polycystic ovary syndrome with this drug (see Chapter 45 on epilepsy in women). In addition, the increased risk of neural tube defects, valproate syndrome and cognitive deficits in children born to mothers taking valproate are issues of concern.

The dilemma of declaring epilepsy on job/college applications may need to be discussed. Although it is important to be honest with a prospective employer, the declaration of epilepsy may prevent short-listing. One option is to leave the appropriate place on the application form blank and, after the candidate has been interviewed and the job has been offered, declare the epilepsy in a positive way. This allows the applicant to explain how the epilepsy should not interfere significantly with their ability to carry out the duties required, and to indicate what measures would be needed if a seizure were to occur at work.

The broad area of ‘independence versus safety’ is difficult for an individual who is trying to establish independence and a smooth transition to adulthood but may need to rely on others to some extent to maintain safety. The specific issue of drowning in the bath must always be discussed in this context. The issue of independence versus safety also impinges on a number of other areas.

Adolescents do not like being told what to do. The doctor should try to avoid giving advice but should instead encourage questioning and provide information, emphasising that the individual is in control of his or her own life. The following are suggested guidelines:

- If possible, talk to the adolescent first, ignoring the parents initially.
- Ask the adolescent to introduce the parents to you.
- Explain to the adolescent what will happen during the consultation.
- Present talking to the parents as ‘a necessary evil’ and explain why this is necessary to the adolescent.
- Write to the adolescent rather than the parents.
- Ask the adolescent’s permission to send copies of letters to the parents.

In addition the following practice points should apply:

- Check the diagnosis.
- Characterise the syndrome.
- Provide accurate prognostic information.
- Treat with appropriate medication.
- Provide information on the following:
 - high risk of the unsupervised bath
 - effect of irregular sleep
 - alcohol
 - driving
 - sport
 - employment
 - contraception
 - genetic implications
 - advantages/adverse effects of specific antiepileptic drugs (AEDs).
- Listen, discuss, inform; avoid giving advice.

Diagnosis

There are several epilepsy syndromes which should not be missed. The following may present in adolescence:

- Juvenile myoclonic epilepsy (JME)
- Juvenile absence epilepsy (JAE)
- Epilepsy with generalised tonic-clonic seizures on awakening
- Benign partial seizures in adolescence
- Photosensitive epilepsy
- Reading epilepsy
- Subacute sclerosing panencephalitis
- Epilepsy from cortical brain tumours.

In addition, seizures from substance abuse or from neuronal antibodies should be considered.

Juvenile myoclonic epilepsy (JME)

JME is an idiopathic generalised epilepsy syndrome with age-related onset, commonly between the ages of 12 and 18 years. The sex distribution is equal. Bilateral, single or multiple irregular myoclonic jerks occur, mainly in the upper limbs. Most of the patients who present for treatment also have tonic-clonic seizures and many have absence seizures. The tonic-clonic seizures predominantly occur soon after awakening.

Patients often present with a history of one or more episodes of tonic-clonic seizures on awakening. The doctor should always ask specifically about morning myoclonic jerks, which, if not severe, may be viewed as slowness or clumsiness. Specific enquiry should also be made about ‘blank spells’. Patients often do not declare myoclonic jerks or absence seizures because they do not realise that these are epileptic seizures but if this information is not available a diagnosis of JME is likely to be missed. It is important to diagnose this condition because most cases respond very well to sodium valproate. This often needs to be continued long term even if the patient is seizure free for years, since the chance of relapse is high if sodium valproate is stopped. The addition of lamotrigine may be effective in those patients who do not respond adequately to monotherapy with sodium valproate. Levetiracetam has been shown to be effective in treating the myoclonic seizures in JME and has a licence for this indication.

Juvenile absence epilepsy (JAE)

The onset of JAE is typically between the ages of 10 and 17 years, with males and females equally affected. Subjects are usually neurologically normal and a family history of epilepsy is common. The photosensitivity rate is high. Over 80% also have generalised tonic-clonic seizures. The absence seizures usually respond well to treatment with anti-absence medication such as sodium valproate, ethosuximide or lamotrigine.

Epilepsy with generalised tonic-clonic seizures on awakening

The peak onset of this syndrome is around puberty. Seizures occur exclusively or predominantly soon after awakening from sleep at any time of the day, with a second seizure peak during evening relaxation. Seizures may be precipitated by sleep deficit, excessive alcohol or sudden arousal.

There is some overlap between these three syndromes. This has generated much discussion on the way in which these three generalised epilepsies should be classified⁷⁸.

Benign partial seizures in adolescence

This syndrome needs to be distinguished from the very different syndrome of benign partial epilepsy of childhood. Age of onset is between 10 and 20 years, with a peak around 13–14 years. It is more common in boys. There is usually no family history and no cognitive or neurological impairment. The subject has simple or complex partial seizures, which can be secondarily generalised. There may be a cluster of 2–5 seizures in a 36–48 hour period. The patient may have only one episode of either a single seizure or a single cluster of seizures. The EEG is typically normal or shows only mild abnormality, in contrast to the syndrome of benign partial epilepsy of childhood, in which centrotemporal (rolandic) spikes occur. Because benign partial seizures in adolescence often present with only one seizure or a cluster of seizures, treatment should be avoided unless there is a recurrence or unless there are particular reasons for treating.

Photosensitive epilepsies

These are more common in adolescence. They are most often detected around 12–14 years of age, although careful history-taking may elicit an earlier onset. Two-thirds of subjects are female. The photosensitive epilepsies do not constitute a single syndrome. It is always important to define the syndrome in which the photosensitive epilepsy occurs, such as JME or JAE, so that specific information on treatment and prognosis can be given.

Reading epilepsy

This is a rare, benign form of epilepsy with a mean age of onset of 17–18 years. It is more common in males. There is a strong genetic predisposition. Diagnosis is confirmed by the very characteristic motor/sensory aura: after reading for a period, abnormal sensations or movements occur (with full consciousness), involving the tongue, throat, jaw, lips and face. If the patient does not stop reading, this aura may progress to a tonic-clonic seizure. If the subject stops reading when the aura occurs, tonic-clonic seizures can often be avoided and treatment with AEDs may not be necessary. If treatment is given then sodium valproate appears to be the drug of choice. The inter-ictal EEG is usually normal.

Subacute sclerosing panencephalitis (SSPE)

This condition, which typically follows measles infection very early in life (under two years of age), usually presents in either in late childhood or in the teenage years with relentless deterioration and eventual death. Initially there may be subtle loss of intellectual ability but myoclonic jerks or more complex abnormal movements soon become evident and the ensuing dementia is all too obvious. The EEG pattern is characteristic, with a discharge in all the leads when each jerk occurs. Measles antibody is raised in blood and is high in cerebrospinal fluid (CSF).

Epilepsy from cortical brain tumours

Cortical brain tumours can occur at any age. Because of this, serious consideration should be given to neuroimaging of adolescents who present with partial seizures. The exception would be those who have characteristic benign partial seizures with a single seizure or cluster of seizures, no abnormal neurological signs and no recurrence.

Investigation

The investigations of epilepsy in adolescence are similar to those at other ages. Basic blood tests for full blood count, creatinine and electrolytes, calcium, and liver function tests should be performed. An EEG with photic stimulation should be obtained. Neuroimaging should be considered but will not be necessary in those conditions which are obviously benign, as described above. In selected cases a urine toxicology screen for substance misuse or testing for neuronal antibodies may be appropriate. The latter may be particularly indicated if the presentation is unusual, especially if there are psychiatric symptoms or other signs of limbic encephalitis¹⁰ (which may or may not be detectable on MRI scanning).

Treatment

It is very important not to group the epilepsies of adolescence together as a single entity. For example, benign partial seizures in adolescence should not be treated whereas treatment of JME with sodium valproate is strongly recommended and often needs to be continued long term.

The mainstay of treatment is with AEDs. First-line drugs, such as carbamazepine and sodium valproate, should generally be used. Sodium valproate is usually effective for JME and for absence seizures. However, valproate is also associated with a risk of neural tube defects and impaired verbal IQ in offspring of mothers who take this drug during pregnancy. It is also associated with weight gain, endocrine problems and fertility problems. Lamotrigine and levetiracetam are being used increasingly as a first-line drugs. They have a wide spectrum of action and are well tolerated. They are not associated with the weight gain and endocrine problems reported with sodium valproate. However, oestrogen decreases lamotrigine blood levels and this interaction may cause problems with oral contraceptives and during pregnancy. For those adolescents with seizures of partial onset who either cannot tolerate the adverse effects of AEDs or refuse to take them, self-control

of seizures can be offered. This method may be effective in suppressing at least a proportion of partial seizures, especially those which are heralded by a clear aura.

In treatment-resistant seizures the possibility of non-epileptic attacks must always be considered and should be managed appropriately with a positive, non-punitive attitude. The concept of 'locus of control' is important. An approach which is often helpful is to say: 'Wouldn't it be wonderful if you were in control of the attacks instead of the attacks being in control of you?' The adolescent should be encouraged to find a way of controlling the attacks. He or she should be reviewed after a specified period of time, for example three weeks. If there is any reduction in the frequency of the attacks he/she should be praised for having done so well and for having begun to gain control themselves. Sometimes a change of life situation may be necessary.

The possibility of seizures precipitated by substance abuse must also be considered, although screening of patients in accident and emergency departments has shown that this is a relatively uncommon cause of presentation with seizures. A number of substances may be associated with the precipitation of seizures in people who do not necessarily have epilepsy. If substances such as alcohol or benzodiazepines are used in large intermittent doses ('bingeing'), then withdrawal effects may precipitate seizures. Seizures as a result of cocaine toxicity have been reported in a number of publications⁹. Ecstasy may also precipitate seizures. If substance abuse is suspected then a urine specimen should be sent for toxicology testing. Hair testing may also be useful in this context. Testing of hair is not of value in the acute situation but can be helpful in determining whether substances have been abused in the recent past and may offer some temporal indication of when the substance misuse took place. Treatment of the underlying substance abuse, rather than the prescription of an AED, is appropriate in these cases.

If the cause of the seizures is neuronal antibodies, for example anti-NMDA receptor antibodies or voltage-gated potassium channel complex antibodies, prompt treatment with immunotherapy can be curative and can also treat, prevent or minimise additional complications.

Surgery may be indicated in a number of circumstances. The most obvious of these is a tumour presenting de novo in adolescence. Some teenagers may have had a history of complex partial seizures for many years and MRI scanning may reveal mesial temporal sclerosis, a dysembryoplastic neuroepithelioma or a hamartoma. It could be argued that these patients should have had surgery earlier. If surgery is necessary, it is probably better to carry this out sooner rather than later. The longer the seizure disorder affects education, development and the social situation, the more difficult it will be to overcome the adverse effects of the epilepsy, even if the seizures themselves are controlled.

Conclusions

Adolescence is an exciting but uncertain period. If epilepsy presents for the first time in adolescence, this adds greatly to complexities of this period. Well-established epilepsy may vary over the course of adolescence, increasing the uncertainty when so many other changes are taking place. When managing epilepsy in adolescence it is important to consider specific syndromes and causes because these may require very different styles of treatment or management. It is also important to consider the impact of epilepsy on the life of the adolescent, and to minimise the isolation and stigmatisation that the teenager may feel at a time when being part of an approving peer group is so important. These factors, together with the issues such as alcohol, driving, sport, contraception, genetic implications and 'safety versus independence', imply that the management of epilepsy in adolescence requires skill and sensitivity.

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CHAPTER 44

Epilepsy and seizures in geriatric practice

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Introduction

With the elderly population (particularly those over 75 years) rapidly increasing, epilepsy in old age is a significant public health issue as well as important clinical problem. Indeed, epilepsy is the third most common neurological disorder in old age after dementia and stroke, diseases which themselves predispose to seizures.

Epidemiology

The incidence of epilepsy follows a bi-modal distribution. The first peak is in the first few years of life whilst a second and more pronounced peak is in those over 60 years old. Indeed, particularly in resource rich countries, the elderly are now the group with the highest incidence of epilepsy in the general population¹. Incidence rates of over 100 per 100,000 for epilepsy in people over 60 years old have been reported². The incidence of acute symptomatic or provoked seizures also rises significantly in older persons³ and the prevalence of epilepsy increases with advancing age, although to a lesser degree.

Aetiology and risk factors

A number of studies show considerable variability in the causes and risk factors for epilepsy^{4–6}. The most frequently reported risk factor is cerebrovascular disease (30–68%), though stroke is responsible for an even higher proportion of cases in which a definite risk factor is identified⁷. Very recent work has suggested that the incidence is higher still in the African-American population although the reasons for this are uncertain⁸. In elderly people with epilepsy, clinically unsuspected cerebral infarcts are often demonstrable on scanning⁹.

Increasingly it is recognised that dementia of all types, but especially Alzheimer's disease (AD), is a common cause of seizures in older age. Patients with early onset AD, for example familial AD with onset in their 50s, may have an 87-fold increase in the risk of seizures compared to age matched controls¹⁰. Even in patients over the age of 65, those with AD are up to ten times more likely to have seizures than those without dementia^{11,12}. Previously it was thought that seizures were likely epiphenomena, simply a consequence of neuronal loss through the hippocampi. More recent work suggests that epilepsy may contribute to the pathogenesis of dementia itself.

Tumours are a less frequent cause of seizures (around 10–15%)^{5,7} and are usually metastatic or aggressive gliomas, though the epidemiological data are inadequate. Meningiomas may mimic transient cerebral ischaemia. Metabolic and toxic causes (e.g. drugs or alcohol) and cerebral hypoxia secondary to the many causes of syncope in old age account for around 10% of all seizures, and a higher proportion of acute symptomatic seizures, in old age. Seizures often have a mixed

aetiology and a minor metabolic insult may trigger epileptic discharges from a pre-existent focus of injury. Other causes of seizures include head injury, infection and, subdural haematoma. Antibody mediated epilepsy (e.g. epilepsy associated with neuronal surface antigens such as leucine-rich glioma inactivated 1 (LGI1) and contactin associated protein like 2 (CASPR2)) is also more common in older patients.

Seizure types and syndrome classification

Focal seizures occur more frequently than generalised seizures (of any type) in old age⁵ but generalised seizure disorders do occasionally first manifest themselves in this age group¹³. Thus, it is not unreasonable to perform EEG recording in this age group to classify seizure type, particularly if there is the possibility of a generalised seizure disorder. EEG may also be required at times if focal onset is suspected when secondary generalisation is the only clinical manifestation.

To date, most studies in the elderly have not used a syndromic classification. Epileptic syndromes that occur commonly in the elderly are:

Remote symptomatic seizures, usually due to precedent stroke or cerebro-vascular disease. Seizures are usually relatively easy to control.

- Acute symptomatic or provoked seizures, possibly due to acute stroke, toxic or metabolic causes (perhaps especially hyponatraemia) or secondary to syncope or cerebral systemic infection. Some people have repeated intercurrent seizures, each related to a recurrent acute situation (e.g. alcohol or hypoglycaemia)
- Progressive symptomatic seizures, usually caused by a tumour or non-vascular dementia
- Cases in which a cause cannot be identified but which are presumed to be symptomatic. Many such cases are believed to be due to occult cerebro-vascular disease
- Late onset generalised seizures are relatively rare in the elderly; the seizures are usually easy to control. People may be misdiagnosed as having non-lesional partial epilepsy. Sleep deprivation EEG studies may be indicated.

Diagnostic pitfalls

As in younger people, the diagnosis of epilepsy is entirely clinical, although circumstances can make it harder to reach that diagnosis in the elderly. Older patients are more likely to present with focal seizures that may have vague manifestations. Owing to relative social isolation, eyewitness accounts are often lacking and differentiating hypoglycaemia, syncope or impairment of cerebral circulation from other causes may be difficult. Recurrent focal seizures are often misdiagnosed as transient cerebral ischaemia if the stereotypical nature of the epileptic symptoms is not recognised. Persistent headache or confusion after an episode of loss of consciousness is suggestive of a seizure.

Older patients may have multiple other co-morbidities making it difficult to disentangle underlying aetiologies. Concurrent disorders that predispose to syncope, e.g. carotid sinus syncope, micturition syncope, and postural hypotension, are common in the elderly. Focal jerking of one arm may occur in tight carotid stenosis. The elderly brain may be more sensitive to a number of external insults. Cardiac arrhythmias frequently present with seizures in the elderly. Conversely seizures of temporal lobe origin may present with autonomic disturbance and cardiac dysrhythmia. Similarly, many older patients are taking multiple medications and as many anti-hypertensives, anti-depressants and

other medications can associate with hyponatraemia, a detailed drug history is essential including the timing of the introduction of new medications.

Post-ictal states in the elderly may be prolonged. Todd's paresis may persist for days and is often misinterpreted as a new stroke. Post-ictal confusion with disorientation, hyperactivity, wandering and incontinence may persist for up to one week, occasionally longer.

Diagnostic difficulties may also arise with neuropsychiatric presentations, e.g. *epilepsia partialis continua* may be confused with an involuntary movement disorder, and the rare paroxysmal sensory epilepsy is often labelled as recurrent transient cerebral ischaemia. However, even after intensive investigations with EEG and 24-hour EEG, diagnostic uncertainty may persist in a considerable proportion of older people.

Prognosis in elderly with seizures and epilepsy

The National General Practice Study of Epilepsy⁷ reported an 80% risk of seizure recurrence in older people at 52 weeks. Remote symptomatic seizures carried a higher risk of recurrence (85%) at three years than acute symptomatic seizures (46%). Other studies have not found older age to be a significant predictor of recurrence^{14,15}. The presence of Todd's paresis or previous acute symptomatic seizures relating to the original insult appears to increase the risk of recurrence¹⁵. A classic study examined prognosis in a large group of elderly admitted to hospital following a seizure¹⁶. Of those not previously treated and observed for at least 12 months, 62% remained seizure free and 26% had less than three seizures per year; 72% of the whole group entered remission within the first year. No controlled clinical trials exist but most studies report that the vast majority of older people with seizures are readily controlled with a low dose of a single antiepileptic drug (AED). A Veterans Administration trial of AEDs in adults showed that a higher proportion of older adults achieved control than did younger adults¹⁷.

Management

As with in all patients with epilepsy, accurate diagnosis is crucial. A trial of an AED is rarely appropriate and a brief period of hospital admission for observation may be useful if the history is unclear.

Identification of the underlying aetiology of seizures is necessary for counselling and may be relevant in deciding future management plans. General management, including reassurance and education for both the person and carer, is crucial. A multidisciplinary approach is helpful: nursing staff are vital in counselling and monitoring the person and an occupational therapist can advise on safety aspects, which may include a home visit, installation of a shower and provision of a personal alarm where appropriate.

There is a lack of relevant data allowing rational therapeutic policies to be made for the treatment of seizures in old age. Information regarding seizure recurrence after an incident seizure and response to AEDs is scant. Such data are necessary to weigh the risks of treatment against the risks of epilepsy and its complications.

Acute symptomatic seizures are most appropriately managed by treating the underlying precipitant (e.g. treatment of infection, correction of metabolic upset, or withdrawal of drug precipitant). In patients with autoimmune epilepsy, immunosuppression should be initiated promptly. AED therapy may be necessary in some circumstances on a temporary basis to suppress seizures while control of the underlying illness is achieved. Advanced age appears to be an independent risk factor for increased mortality in status epilepticus, and this should therefore be treated vigorously.

The approach to treatment of a first unprovoked seizure in an older person is more contentious. Such people are often classifiable as having remote symptomatic seizures secondary to a cerebral infarct. Treatment to prevent serious injury and the dangers of prolonged post-ictal states may well be justified after a first generalised seizure on the basis of a persisting, epileptogenic focus. However, some such seizures may be erroneously classified as remote symptomatic if a concurrent acute vascular event is clinically silent. It is important to discuss with patients the risk of seizures and the potential side effects of medications so that an informed decision can be reached together. Similarly, it is essential that vascular risk factors are addressed to prevent further cerebral insult.

Recurrent unprovoked seizures clearly require treatment. Potential first-line broad-spectrum AEDs that may be used in the elderly include lamotrigine, levetiracetam and less so sodium valproate or gabapentin. Comparative trials in older persons are, however, few. A multicentre trial comparing sodium valproate and phenytoin suggested both agents were useful first-line drugs¹⁸. A higher rate of failure occurred for people receiving phenytoin (poor control 6%, adverse events 14%) than sodium valproate (poor control 1%, adverse events 9%) although the differences were not significant. A study assessing the impact of sodium valproate and phenytoin on cognitive function found no difference between the drugs in a group of elders^{19,20}. Frequent non-cognitive side effects were, however, reported. Trials have also shown no difference of efficacy between lamotrigine, carbamazepine and gabapentin²⁰⁻²².

AED pharmacokinetics may be altered by age. It should be emphasised that inter-individual variability may be much more important than changes associated with age alone^{23,40}. Moreover, many older patients are taking multiple other medications. Tailoring of the dose with regard to concurrent illness and drug treatment is paramount to avoid toxicity.

Which AED?

AEDs should be introduced cautiously in the older population and generally start at half the dose that is initiated in those under the age of 65. Titration is also slower, and the initial ceiling dose should also be lower than in younger patients. Elderly patients may, for example, maintain seizure freedom with Lamotrigine 25mg bd.

Phenytoin is not an AED for long term prescribing in epilepsy. Although potential advantages include once-daily dosing, low cost and ready availability in parenteral form, disadvantages are much more significant. Difficulties include non-linear kinetics, such that small alterations of dosage may produce plasma concentrations associated with toxicity or inefficacy. Increased free concentration of phenytoin with neurotoxicity may occur when plasma albumin falls, particularly during acute illness. As in younger people, seizure control is frequently achieved in people with plasma concentrations below the quoted range. Concentration-dependent neurotoxicity may be experienced more frequently and at more modest plasma concentrations in older people. As an enzyme inducer, Phenytoin may significantly interact with other medications. Moreover, Phenytoin may cause metabolic bone disease, folate deficiency, balance difficulties and neuropathy – all of which may be particularly problematic in this age group.

Carbamazepine, an enzyme inducer, is a possible, but not preferred, option in the treatment of epilepsy in the older person particularly if there is no associated co-morbidity. Sedative effects may limit tolerability but can be minimised by starting with a very low dose and slow upward titration. Intra-dosage variation in concentrations of carbamazepine, which are related to the extent of autoinduction of metabolism²⁵⁻²⁶, appears to be rather less in the frail elderly. Once or twice-daily dosing with conventional carbamazepine tablets is sufficient for most. While the overall risk of bone marrow suppression and hepatitis is small the incidence may be increased by age.

Carbamazepine has an antidiuretic hormone-like effect, and this may produce fluid retention and precipitate cardiac failure. Mild hyponatraemia is usually asymptomatic but profound reductions in serum sodium may occur during intercurrent illness or during concomitant treatment with thiazide diuretics. Carbamazepine may precipitate problems with cardiac conduction in elderly people with pre-existent cardiac disease. There are also concerns about its potential effects on bone health. **Oxcarbazepine**, a carbamazepine like pro-drug that avoids epoxidation, would be an alternative but there is no definitive data regarding its use in this age group and there are concerns particularly with its propensity to cause hyponatraemia. **Eslicarbazepine** may show more promise in this older age group although research is required to investigate this thoroughly.

Sodium valproate can be well-tolerated and effective in older people. It is a preferred medication for some epileptologists. Unlike phenytoin and carbamazepine, it is not an enzyme-inducing drug and is less susceptible to involvement in drug interactions. However, sodium valproate can have significant side effects. Sedation, cognitive slowing, tremor and gastrointestinal disturbances are the most frequent limiting adverse effects. Cognitive slowing usually improves on dose reduction, but it can be so severe in some older people that the drug may have to be withdrawn. The effect on cognition may be secondary to hyperammonaemic encephalopathy and it is therefore worth checking a serum ammonia level and treating with lactulose should the ammonia level be high. Valproate can also have an adverse impact on bone health.

Lamotrigine is a first-line drug in this age group, particularly in view of its overall good tolerability. It does not exhibit auto-induction, is not an enzyme inducer and has little effect on cognition. It does, however, have the potential to cause idiosyncratic skin reactions and, very occasionally, more severe reactions. Another problem in this age group is its propensity to cause insomnia and tremor. If insomnia proves difficult then switching drug intake to an earlier time may be helpful. Lamotrigine can be initiated very slowly, for example 12.5mg nocte to increase in 12.5mg steps at intervals of not less than two weeks to an initial ceiling dose of Lamotrigine 25mg bd.

Levetiracetam is also a first-line drug in this age group, particularly in view of its overall good tolerability and clean pharmacokinetic profile. In a subset analysis of the KEEPER, Levetiracetam seemed to be particularly effective in older patients²⁸. It has, however, the potential to cause lethargy and irritability which may be more pronounced in some older people. Similarly, the rate of introduction of Levetiracetam can be very gradual, for example 125mg nocte to increase in 125mg steps at intervals of not less than two weeks to an initial ceiling dose of Levetiracetam 250mg bd.

Lacosamide may be considered in older patients as it too has few drug interactions, appears to have no significant adverse effect on cognition. There is a possibility of Lacosamide causing palpitations and therefore an ECG before initiation is recommended. Similarly, one may be mindful of prescribing Lacosamide in those with pre-existing cardiological conditions.

Gabapentin is relatively infrequently prescribed as an anti-epileptic medication although it is frequently prescribed as a neuromodulator to older people and may have a specific role in helping control seizures in the elderly²⁹. It again has limited drug-drug interaction, has no significant adverse effect on cognition and is generally well tolerated.

Overall, the current treatment choice for chronic treatment of older people with epilepsy probably rests with low-dose monotherapy with Lamotrigine, Levetiracetam or Gabapentin. Lacosamide, Sodium Valproate and possibly Carbamazepine are alternatives. Topiramate and perhaps Zonisamide are somewhat less favoured owing to potential impact on cognition and other side effects. There are limited data on the very novel anti-epileptic medications, for example Perampanel or Brivaracetam, in the elderly. Phenytoin should overall be avoided.

Whichever drug is used the introductory dose should be low and dose titration should be slow and cautious. Monitoring for potential side effects should be intensive and due consideration should be given to the presentation of non-specific side effects of AEDs, for example falls, confusion, incontinence. Therapeutic ranges are less helpful in elderly people.

Epilepsy surgery in older patients

Older patients with pharmacoresistant epilepsy are less likely to undergo epilepsy surgery which may reflect patient choice, physician choice or both³⁰. Many centres do not offer epilepsy surgery to patients over 75 years of age. However, as the population ages distinctions will be made between biological and chronological age.

Epilepsy surgery in older patients can associate with reduced likelihood of seizure freedom and increased rate of complications^{31,32}. However, this is not universal: some centres have reported similar rates of post-operative seizure control and complications in patients over 50 versus their younger counterparts³³. Cognitive risks also exist. When older patients aged 50–69 (N=55) were compared to patients aged less than 50, seizure freedom rates at one year were reported to be similar³⁴. However, the rate of post-operative cognitive impairment was substantially higher in older individuals, particularly those undergoing left temporal lobectomy. Furthermore, older patients undergoing epilepsy surgery had lower pre-operative memory performance than younger surgical candidates. Therefore, the potential adverse cognitive effects of epilepsy surgery must be carefully considered in the elderly as reduction in cognitive function in individuals with poor reserve could precipitate significant difficulties in daily life. These findings may not apply to all cases and the underlying pathology might be important. For example, when patients with hippocampal sclerosis were examined at a single centre, operated on by the same surgeon utilising the same operative technique, no difference in post-operative outcome in terms of either seizure control or cognitive impairment was found between patients older than 50 (N=21) compared to those under 50 (N=109)³⁵. Very limited data on vagal nerve stimulation in the elderly exist.

Co-morbidity in older patients

Patients with epilepsy are prone to cognitive and psychological co-morbidity. The condition also associates with psychosocial difficulties. All three of these aspects are exacerbated in older patients with epilepsy. Often an underlying illness (stroke, dementia) is responsible for the development of seizures and older patients with epilepsy are more likely to have significant systemic co-morbidities than their younger counter-parts. Moreover, depression, which may increase cognitive difficulties, can be compounded by the social isolation of, for example, not being able to drive at an age where it may not be possible to easily access public transport.

Conclusion:

Epilepsy is already very common in the older population and the incidence will rise as populations age. Diagnosis can be difficult but, as for all epilepsy, rests on securing a detailed history. Ancillary tests can be non-contributory and occasionally confusing. Lamotrigine and Levetiracetam are preferred medications in this age group and in those with pharmacoresistant seizures, surgery can be considered. In particular, the intersection of aetiologies of epilepsy in this age group and co-morbidities requires ongoing study.

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CHAPTER 45

Epilepsy and women

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Women with epilepsy, of all ages, have unique therapy considerations, that that should be kept in mind, to achieve optimal care. It becomes particularly relevant at the pre-transition phase of care, as antiepileptic drug (AED) therapy selected in childhood may influence choices in adult life. From the time of diagnosis, the following important issues should be considered:

- Female hormones and seizure control
- treatment of catamenial epilepsy
- Fertility
- Contraception
- Pregnancy
 - the effects of epilepsy and AEDs on pregnancy
 - the effects of pregnancy on AEDs and seizure control
 - the effects of epilepsy and in particular, seizures on the developing embryo/foetus
 - the effects of AEDs on the developing foetus/embryo
 - management of labour and postpartum management of mother and child
 - pregnancy and mortality risk
 - psychiatric wellbeing in pregnancy
- Epilepsy and the menopause
- AEDs and physical appearance

Female hormones and seizure control

Epilepsy and AEDs are associated with changes in female hormones that may result in menstrual irregularity, reproductive problems and abnormalities of bone health. Female hormones may also affect seizure threshold, resulting in increased frequency of seizures at certain times of the menstrual cycle.

Hormonal alterations, including changes in prolactin, follicle-stimulating hormone and luteinising hormone have been observed following generalised and focal seizures¹. They are thought to arise because of connections between the hypothalamic-pituitary axis and areas of the brain involved in seizures, although the precise mechanisms are unclear¹⁻³. These hormonal problems can result in reproductive dysfunction, with the most common disorders being polycystic ovarian syndrome (PCOS) and hypothalamic amenorrhoea^{1,4}. It is estimated that PCOS occurs in 20% of women with epilepsy, compared to 5% of those without. However, this relationship is complicated by the potentially confounding effects of AEDs, in particular valproate which will be outlined later.

An increase in seizure frequency around the time of menstruation (catamenial epilepsy) was first clinically documented by Gowers in 1881 but cyclical variations in seizure frequency have been known about since antiquity and were initially attributed to the cycles of the moon.

There is no agreement on the degree of seizure exacerbation required to meet a definition of catamenial epilepsy. Various authors have reported an increase in seizures perimenstrually, however many of these studies are poorly documented, use a less than strict definition of what seizures to include in the calculation of perimenstrual attacks and are unrepresentative of the female population with epilepsy. Using the strict definition for catamenial epilepsy that $\geq 75\%$ of seizures have to occur within four days preceding and within six days of the onset of menstruation, Duncan *et al*, showed that only 12.5% of 40 women met this criterion⁵. However, 31 (78%) claimed that most of their seizures occurred around the time of menstruation.

Experimental evidence from animal studies suggests that the change in seizure frequency during the menstrual cycle may be related to fluctuations in the neuroactive effects of relative oestrogen and progesterone concentrations, with oestrogens exhibiting proconvulsant properties and progestogens having anticonvulsant effects⁶. Human data tend to support this hypothesis, although there appear to be no clear differences in hormonal changes in women with and without catamenial seizures⁷. Physiological changes to gamma-aminobutyric acid A (GABA_A) receptor function as a result of progesterone and its active metabolite allopregnanolone withdrawal at the time of menstruation (day 25 of the outgoing cycle to day 3 of new cycle) provide one possible mechanism for exacerbation of seizures perimenstrually (which is the most common type of catamenial seizure exacerbation), although other mechanisms have also been suggested⁸.

The second most common pattern observed is the periovulatory pattern, where increased seizure frequency has been reported when oestrogen concentrations are highest (d10 to d15)⁹. Anovulatory cycles tend to be associated with higher seizure frequencies, in particular during times of peak oestrogen concentration¹⁰. Anovulatory cycles tend to be associated with an increase in seizure frequency in the second half of the menstrual cycle while ovulatory cycles can have one or two peaks in seizure frequency, at around the time of menstruation and/or ovulation¹¹.

Other influences around the time of menstruation, such as premenstrual tension and mood changes, may also be important and may have an effect on seizure control. Premenstrual tension is more common in women with catamenial epilepsy (75%) compared with other women with epilepsy (43%)¹².

Treatment of catamenial epilepsy

Over the last century many therapeutic agents have been tried with various degrees of success. Bromides were introduced by Locock in 1857 for the treatment of “catamenial” and “hysterical epilepsies.” By the turn of the century, it had been noted that seizure frequency occasionally decreased at the menopause or after oophorectomy. In the 1950s acetazolamide became available, which is advocated by some for use in catamenial epilepsy (250–500mg daily for 3–7 days prior to menses). Data, on which this supposition is based are scant, with no randomised controlled trials and conflicting views on its effectiveness^{13,14}.

Over the last decade or so, one of the main areas of therapeutic research has been hormonal manipulation. Here the aim is either to increase relative progesterone concentrations or to convert anovulatory to ovulatory cycles^{15,16}. In an open study of progesterone therapy in 25 women with catamenial epilepsy 72% experienced a decline in seizure frequency¹⁷. Reports suggest that the reduced metabolite of progesterone, tetrahydroprogesterone (allopregnanolone), rather than progesterone itself, is responsible for improved seizure control^{18–20}, through modulation of GABA_A chloride conductance²¹.

Other approaches have involved the intermittent use of AEDs perimenstrually. Many of the problems of tolerance, in particular those of benzodiazepines, can be overcome using this treatment model.

In a double-blind crossover study of 20 mg clobazam versus placebo over a predetermined ten-day period in each menstrual cycle, clobazam was found to be superior to placebo in 14 women (78%) and completely prevented catamenial seizures in the majority²².

With regard to therapy it should first be established whether the seizures are truly catamenial, and the particular subtype of catamenial epilepsy, and that the menses are following a regular pattern²³. If so, intermittent therapy with clobazam 10 mg at night perimenstrually is the simplest and most useful therapy for the majority of women. If this fails, it may be worth considering the use of acetazolamide perimenstrually or increasing the dose of the AED around the time at risk. Finally, hormonal manipulation could be considered with medroxyprogesterone or clomiphene²⁴. However, good evidence for the effectiveness of these therapeutic options is lacking. A secondary analysis of a randomised controlled trial of progesterone for catamenial epilepsy identified progesterone lozenges (200mg TDS) between days 14–28, as being useful at reducing perimenstrual seizure exacerbations²⁵.

Fertility

It has been suspected for some time that women with epilepsy have reduced fertility. The potential reasons are likely to be complex, including biological, psychological, social and economic factors. It has also been reported that sexual arousal may be reduced in women with epilepsy. Conflicting studies have been published on the issue of fertility in women with epilepsy.

There is a high incidence of menstrual disorders among women with epilepsy²⁶. Over 35% of women with temporal lobe epilepsy had anovulatory cycles when studied over three cycles, compared to 8% of controls²⁷. Treatment with progesterone suppositories in the appropriate phase of the menstrual cycle²⁸, clomiphene²⁴, and medroxyprogesterone¹⁷, have been met with some success.

A prospective study from the Kerala Registry of Epilepsy and Pregnancy showed that women with epilepsy have an increased risk of infertility, particularly if they are using polytherapy. Infertility was least (7.1%) for those with no AED exposure and higher (P = 0.001) for those with AED exposure (31.8% with one AED, 40.7% with two AEDs and 60.3% with three or more AEDs). In this study women with epilepsy exposed to phenobarbital had significant risk of infertility, but no such trend was observed for valproate or other AEDs²⁹.

Particular emphasis has been placed on valproate. In 1993, Isojarvi reported that polycystic ovaries and hyperandrogenism are frequently detected in women on valproate³⁰. Subsequently they reported that these abnormalities are more common in women on valproate who gain weight³¹, especially if this is during pubertal maturation³². However, their initial study was retrospectively based in a selected population and did not concentrate on clinical endocrine status. More recently, studies have been conflicting, reporting both significant associations between valproate and PCOS and reporting no significant associations. Betts *et al* have shown that women who had taken valproate for at least a year were more likely to have biochemical evidence of hyperandrogenaemia than those who had taken carbamazepine or lamotrigine³³. However, others have not been able to replicate their results, reporting that the occurrence of polycystic ovaries in women taking AEDs is not higher than the general population³⁴. The occurrence of polycystic ovarian syndrome (PCOS), which is associated with menstrual disturbance, has also been shown to be similar for women with epilepsy taking either carbamazepine or valproate, and similar to women with epilepsy on no treatment³⁵. Furthermore, a subsequent study performed in monkeys did not indicate that exposure to valproate for 12–15 months induced hormonal or morphological ovarian abnormalities or characteristics of PCOS³⁶. Morrell *et al* conducted a recent prospective, randomised, longitudinal evaluation for the impact of valproate on the development of PCOS. Women with epilepsy and regular menstrual cycles were randomised to treatment with valproate or lamotrigine and followed

up for 12 months. Women taking valproate were significantly more likely to develop PCOS than those taking lamotrigine (9% vs. 2% respectively, $P = 0.007$)³⁷. These observations, together with data showing that valproate associated changes are reversible when valproate is discontinued^{38,39} suggest that a reasonable treatment option in women who develop PCOS and/or ovulatory dysfunction while taking valproate is to consider discontinuation of the drug and treatment with an alternative AED, if possible.

A well designed, prospective case-control study (Women with Epilepsy: Pregnancy Outcomes and Deliveries [WEPOD]) assessed time to pregnancy in WWE. Eighty-nine WWE and 108 controls without epilepsy were enrolled. Pregnancy was achieved by 61.4% WWE compared with 60.6% for controls, with no significant difference at one year. Nor was there a significant difference in median time to achieve pregnancy, or number of live births⁴⁰.

Contraception

The risk of unplanned pregnancy may be as high as 65% in WWE⁴¹ compared with 50% in the general population⁴². It is clear that family planning information at the correct time, to allow women to make safe and efficacious contraception choices in the context of their AED treatment is vital. The highest risk of unplanned pregnancies is in those under eighteen, highlighting the relevance of this issue during transition⁴³.

Various contraceptive options exist for WWE. Bidirectional interactions can occur with hormonal contraception and AEDs. In an attempt to understand the contemporary use of contraception in women with epilepsy a retrospective, self-reported, web-based study -the Epilepsy Birth Control Registry (EBCR) was set up which surveyed 1144 WWE and found that IUDs had the lowest failure rate⁴¹, compared with the withdrawal method, barrier contraceptives, and hormonal contraception. Systemic hormonal contraception varied in terms of failure rate, depending if oral (greater failure) or non-oral forms were used, and in relation to the AED used (enzyme inducing had a greater failure rate). They also demonstrated a greater increase in seizures with the use of hormonal contraception (18%) compared with non-hormonal contraception (4%)⁴⁴. This work needs prospectively replicated.

The EBCR reported that 41% of women with epilepsy discontinued their contraceptive method during the time of the study. Hormonal contraception was the most discontinued therapy (50.7%) and IUDs were the least discontinued contraceptive method (25.1%). Contraceptive therapy was discontinued for three main reasons; reliability concerns in 14%, menstrual problems in 14%, and increased seizures in 9%⁴⁵.

Having epilepsy should not restrict the use of contraception, however hormonal methods of contraception and AEDs may interact. It has been suggested that WWE should be advised to use long-acting reversible contraception (LARC) and that this should be promoted by the epileptologist/neurologist⁴⁶.

The AEDs phenobarbital, primidone, phenytoin, carbamazepine,⁴⁷ topiramate⁴⁸ and eslicarbazepine acetate are inducers of the hepatic P-450 microsomal isoenzyme CYP3A4 which is responsible for the metabolism of oestrogens and progestogens. This results in an increased metabolism of the combined oral contraceptive pill (OCP), which may lead to a higher rate of breakthrough bleeding and contraceptive failure. Sodium valproate and the newer AEDs, vigabatrin, gabapentin, tiagabine, pregabalin, levetiracetam, lacosamide, and zonisamide do not induce hepatic enzymes and hence do not react with the OCP. Topiramate is a less potent inducer of hepatic enzymes, and this effect seems to be dose dependent. In monotherapy, doses less than 200mg did not

significantly alter the pharmacokinetics of the combined oral contraceptive pill containing 35 micrograms of ethinylloestradiol⁴⁹. Oxcarbazepine is also considered a weak enzyme-inducing agent as is eslicarbazepine (S-enantiomer of the active component in oxcarbazepine, perhaps having a slightly lower theoretical risk)⁵⁰.

The situation for lamotrigine is less clear. While initially not thought to interfere with the OCP, there is one report in which lamotrigine was associated with a small decrease in the levels of the progestin used in this study, levonorgestrel, with the AUC reduced by 19% and maximal concentration by 12%⁵¹. As a result of this data, the manufacturer of lamotrigine released new guidance and the Summary of Product Characteristics (SPC) now comments that 'the possibility of reduced contraceptive effectiveness cannot be excluded'. It suggests that 'the use of alternative non-hormonal methods should be encouraged' and, 'a hormonal contraceptive should only be used as a sole method of contraception if there is no other alternative'. A statement regarding this change was issued by the Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit, concluding that there was 'no evidence that lamotrigine reduces the effectiveness of hormonal contraceptives' and that 'there is no good evidence to suggest that non-hormonal methods should be used in favour of hormonal methods'⁵². Further studies in larger numbers of women are needed to clarify this possible effect.

The manufacturers of perampanel state that it is not a strong inducer or inhibitor of cytochrome P-450. However, evidence exists to show that concomitant use of the OCP with perampanel 12 mg dose per day can result in reduction in levonorgestrel levels (AUC and mean peak serum concentration reduced by 40%), and an 18% reduction in the mean peak serum concentration of ethinylloestradiol, potentially resulting in reduced efficacy of progesterone-containing oral contraceptives. This effect was not observed at 8mg doses or below⁵³.

It is recommended that women taking enzyme-inducing AEDs increase their ethinylloestradiol dose from 20-35 µg to 50 µg. If breakthrough bleeding occurs ethinylloestradiol dosages may need to be increased to 75 or 100 µg or the 50 µg pill may be tricycled (three packets taken continuously, then a four-day break). Women also need counselling that even on a higher dose combined OCP, efficacy may be reduced. Breakthrough bleeding occurring in the middle of a cycle of contraceptive use is generally due to a relative oestrogen deficiency and usually taken as a sign of incipient failure of contraception⁵⁰. However, pregnancy rates (approximately 7% per year) still appear to be lower compared with barrier methods which have a failure rate of between 15 and 20%.

Levonorgestrel implants have an increased failure rate in women taking enzyme-inducing AEDs⁵⁴, and although the data are not available it can only be assumed that the efficacy of progesterone only OCPs is also reduced. Medroxyprogesterone injections may be effective in women with epilepsy, with their elimination being dependent on hepatic blood flow instead of hepatic metabolism, but data proving this are not as yet available. Whether the dose of the morning-after pill should be changed in those on enzyme-inducing drugs is unknown.

Of note, OCPs can reduce the levels of lamotrigine and to a clinically significant level⁵⁵ through inhibition of CYP enzymes and by UGT enzyme induction. Both valproate and lamotrigine serum levels are reduced when taken alongside the combined oral contraceptive pill, via enhanced glucuronidation. The clinical relevance of the effect on valproate is not certain, but it is clinically significant with lamotrigine (>50% drop in serum levels reported). Data to date don't indicate significant effects of the combined oral contraceptive pill affecting levetiracetam lacosamide, or zonisamide metabolism.

Pregnancy

The management of pregnant women with epilepsy is becoming of increasing importance as the risk factors for adverse outcomes of pregnancy become more clearly delineated⁵⁶⁻⁶¹. The increasing evidence base for management has also resulted in expert and national groups forming guidelines to aid management. The majority of women with epilepsy will have a normal pregnancy and delivery with unchanged seizure frequency. Considering the prevalence of epilepsy many pregnancies are still at risk for an adverse outcome, and pregnancies in women with epilepsy are considered high risk and need careful management by both epilepsy and obstetric specialists.

Preconception Counselling

Preconception counselling should be available to all women with epilepsy contemplating a pregnancy. This should start at the time of diagnosis and at subsequent reviews. These issues can be discussed initially in the early teenage years, depending on the level of maturity of the young woman. Women do not always recall being given relevant information, with one postal survey finding less than 50% recalling salient information related to epilepsy and pregnancy⁶². It should therefore be clear this information needs to be repeated regularly (ideally at least annually).

A joint obstetric/neurology pre-conceptual counselling service is one model of service delivery which allows robust assessment for those contemplating pregnancy, ideally the same team subsequently coordinate care during pregnancy⁶³.

During counselling a re-evaluation of the diagnosis and the need for continued antiepileptic medication should take place. Consideration should be given to the AED choice and dosage. The risks and benefits of reducing or changing medication should be explored. MCM risks should be discussed and compared to the general population (2-3%). The spectrum of malformations occurring with specific AEDs should be discussed. The risks of cognitive and developmental delay are important to discuss, including an acknowledgement of limited knowledge for many AEDs. This all must be balanced with the risk of seizures and complications of seizures including SUDEP. Emphasising medication adherence, providing folic acid supplementation and offering general health advice such as weight management, smoking cessation, and how to maintain health levels of exercise should all be covered.

Prior pregnancy outcome is important to consider during pre-conceptual counselling; some evidence suggests women with past pregnancies with MCM are at higher risk of MCMs in future offspring. Small studies of infants with foetal anticonvulsant syndromes quoted this risk as between 39% and 55%, but more recent studies have estimated the recurrence risk of major malformations as between 15.8% and 35.7%. In studies by the UK Epilepsy and Pregnancy Register⁶⁴ and the Australian Register of Antiepileptic Drugs in Pregnancy⁶⁵ the recurrence risk for congenital malformations was higher for women taking valproate (21.9% and 57.2%) than for those on other AEDs. Women attending for pre-conceptual counselling who have had a previous child with a major malformation, particularly on valproate, should be informed that they may have a higher risk of major malformations in subsequent pregnancies if the AED/dose of valproate is not changed. The magnitude of this increase in risk remains to be clarified.

Parents are also concerned regarding the risk of epilepsy in the child. The risk is dependent on the type of seizure disorder and the number of affected relatives. For primary generalised epilepsy, there is up to a 10% chance of offspring developing epilepsy, which is increased if both parents have epilepsy or if the child's siblings develop epilepsy. The risk is lower if only the father has epilepsy compared with if only the mother has epilepsy⁶⁶. The genetics of the seizure disorder may

also need to be taken into consideration. E.g. In autosomal dominant conditions such as tuberous sclerosis there is a 1:2 risk inheritance. A Danish population based register study found an excess risk of epilepsy in those born to mothers younger than 20 years of age (HR = 1.17; 95% CI 1.07-1.29) and those where the paternal age was greater than 5 years older than the maternal age. This risk increased with the size of the gap, and those of 15 years or greater age gap has adjusted HR 1.28; 95% CI 1.16-1.41⁶⁷.

Folic acid

The prescription of folic acid before conception and at least until the end of the first trimester is recommended in patients taking antiepileptic medication, as it is for all women. This followed the recognition that there is an increased risk of neural tube defect in children born to mothers taking AEDs, in particular sodium valproate and carbamazepine⁶⁸⁻⁷⁰. Large community-based studies have demonstrated a reduction in the rate of neural tube defects in women taking folic acid pre-conceptually⁷¹⁻⁷³. It has been inferred from this that folic acid will protect women with epilepsy who are also at increased risk of this complication. The optimum dosage of folic acid remains undetermined. Community-based studies have used dosages ranging from 0.5-4.0 mg daily, the higher dosage being suggested for women considered at higher risk. It is the higher dosage that is generally recommended in the UK guidelines for women with epilepsy (5 mg daily).

Some concerns have been raised that folic acid may exacerbate seizures, but these fears have generally been felt to be unfounded. There is as yet no direct evidence that folic acid will protect against the neural tube defects or other malformations seen in association with AEDs. There is some evidence that the neural tube defects which occur in association with sodium valproate are somewhat different from those seen in the general population. They tend to be low lumbar or sacral in site⁷⁴. Other abnormalities are less common, and the defect may be the result of altered canalisation rather than folding of the developing neural crest. It remains uncertain as to whether folic acid will protect against this form of neural tube defect⁷⁵, or other defects associated with AEDs⁷⁶. The potential effect of folate supplementation was reported for 4680 cases from the UK Epilepsy and Pregnancy Register⁷⁷. Those patients who received pre-conceptual folic acid, approximately three-quarters of whom received 5 mg each day, appeared more likely to have a child with a major congenital malformation than those who did not (3.9% vs 2.2%; odds ratio 1.8 [95% CI. 1.2-2.5]). However, peri-conceptual folic acid was associated with a reduction in the incidence of valproate-associated neural tube defects (0.8% vs 1.6%). The EURAP pregnancy registry has reported similar findings, with folic acid use three months prior to conception and in the first trimester carrying an odds ratio of 1.4 (95% CI 1.02-1.82, P = 0.035) of major congenital malformations over those not adhering to this regimen⁷⁸. While the above results clearly do not mean that we should stop prescribing folate peri-conceptually to women with epilepsy they do question the validity of this approach for reducing the risk of major malformations.

Periconceptual folic acid supplementation is associated with a lower risk for the development of autistic traits in AED exposed pregnancies. The critical time for folate supplementation to reduce language delay (up to 36 months), in AED-exposed cases was from 4 weeks pre-conception until the end of the first trimester. No clear correlation between folic acid dose and plasma folate concentrations were noted^{79, 80}.

Recent data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group has suggested that peri-conceptual folic acid may have a positive effect on mean IQ in infants exposed to AEDs in utero⁸¹. In this study of 225 children, peri-conceptual folic acid was associated with higher child IQ at age six (mean IQ 108 vs. 101, P = 0.0002). This effect was seen across all AEDs studied (carbamazepine, lamotrigine, valproate and phenytoin). Together with results from studies in the general population showing reduced risk of severe language delay with folic

acid supplementation in early pregnancy⁸², and improved measures of verbal communication with pre-conceptual folic acid at high dose (5 mg daily)⁸³, these data would suggest that it may be of benefit to continue high dose folic acid supplementation throughout pregnancy.

The effects of epilepsy and AEDs on pregnancy

Data on whether women with epilepsy are at increased risk of obstetric complications are unclear. Complications that have been reported as being increased compared with control mothers are vaginal bleeding, spontaneous abortion, pre-eclampsia, and premature or prolonged labour⁸⁴. Higher frequencies of labour induction and artificial labour have also been reported⁸⁵, but whether this is due to a greater frequency of medical indications or is due to increased concern on the part of obstetricians or mothers-to-be is uncertain⁸⁶.

The adverse outcomes most consistently reported are increased stillbirths and neonatal deaths^{87,88} although there is some evidence that the latter has been improving⁸⁹. Data on whether women with epilepsy are at increased risk of early pregnancy loss are conflicting. A recent population-based study from the Danish Medical Birth Registry identified a 13% increase in risk of spontaneous abortion in women taking AEDs during pregnancy. However, no increase in risk was seen when this analysis was limited to women with epilepsy, suggesting this effect may be due to confounding factors rather than seizures or AEDs⁹⁰. Clearly research into early pregnancy loss is difficult and the authors highlight that this study was designed to look only at clinically recognized pregnancies. If AEDs consumption caused an increase in very early spontaneous abortion, this would not have been identified. The retrospective Epilepsy Birth Control Registry, found that the risk for spontaneous fetal loss in 653 women with epilepsy was significantly greater for unplanned (n=137 of 391; 35.0%) than planned (n=43 of 262; 16.4%) pregnancies (RR, 2.14; 95% CI, 1.59–2.90).⁹¹

EURAP reported on 7055 pregnancies in which 632 ended in intrauterine loss of the foetus (592 spontaneous abortions and 40 stillbirths). The rate of intrauterine death from monotherapies was 8.2%; (95% CI: 7.5–8.9), and for polytherapy was 12.1% (95% CI 10.5–13.9%). The most important risk factors for intrauterine death were exposure to AED polytherapy and parental MCM history⁹². The Australian Register of Antiepileptic Drugs in Pregnancy (APR) found that AED receiving women who had a spontaneous abortion in a previous pregnancy had a 2-3-fold higher risk of the same in a future pregnancy when compared with women who did not have a previous abnormal outcome⁹³.

Since 1958 over 40 cases of neonatal bleeding associated with maternal AED treatment have been reported⁹⁴. It is felt that this is due to reduced clotting factors, consequent to alterations in vitamin K metabolism, in infants exposed to enzyme-inducing AEDs, such as phenytoin, phenobarbitone and carbamazepine. There is evidence that newborn infants that have been exposed to enzyme-inducing AEDs in utero may show increased levels of PIVKA II (protein induced by vitamin K absence of factor II), an indirect marker of vitamin K deficiency^{95,96}. While there is no evidence directly linking this biochemical marker to a clinically increased risk of bleeding in the neonate, its suppression with vitamin K₁ supplementation given as 10 mg orally each day from the 36th week of gestation⁹⁷ has resulted in most guidelines for best practice advocating maternal supplementation with vitamin K₁, with all infants also being given 1 mg vitamin K₁ intramuscularly at birth^{98,99}. However, the results from a recent case-control study did not show that there was an increased risk for bleeding in infants exposed in utero to enzyme-inducing AEDs (mainly carbamazepine and phenytoin)¹⁰⁰, although it was felt that supplementation might be necessary in selected cases, such as when prematurity is anticipated. Nevertheless, although the risk of haemorrhagic disease of the newborn is small, early UK and other best practice guidelines recommended the prescription of 10–20 mg/day of vitamin K given orally to women with epilepsy in the last month of pregnancy^{98,99}, especially if an enzyme-inducing AED is being taken. However, the American

Academy of Neurology updated its practice parameter in 2009, stating that there was insufficient evidence to determine if infants born to women with epilepsy had increased risk of haemorrhagic complications, or if prenatal supplementation of vitamin K reduced these risks⁵⁹. At present it is not possible to give oral supplementation in the UK as there is no orally available preparation of vitamin K which can be prescribed in pregnancy. At birth it is recommended, as is the case for all newborns, that infants receive vitamin K, with 1 mg of vitamin K given intramuscularly^{98,99}.

The effects of pregnancy on AEDs and seizure control

Epilepsy which is well controlled before pregnancy has a high likelihood of remaining well controlled during pregnancy. The EURAP study (n=1956) showed that using the first trimester as a reference, seizure control remained unchanged throughout pregnancy in 63.6% and of those 92.7% were seizure free during the entire pregnancy¹⁰¹.

Fear of adverse fetal events, or poor tolerance due to nausea can result in poor concordance with therapy, resulting in loss of seizure control. Measuring compliance is problematic and monitoring serum levels or self-reporting may not be reliable. A study comparing longer term AED ingestion in pregnant and non-pregnant women using hair samples found 15% of the cohort of pregnant women having little or no AED in their proximal compared with distal hair measurements of AEDs¹⁰². The WEPOD study using an electronic diary, that was completed daily, found medication compliance was self-recorded at 97% overall, with 44% admitting missing medication on one day¹⁰³. This may represent a selection bias regarding the study design.

During pregnancy total serum AED levels may fall with less marked reductions in non-protein bound (free) drug concentrations^{104,105}. Many factors may contribute to this fall including increased metabolism/excretion, increased plasma volume and reduced protein binding. Total AED concentrations do not predict response during pregnancy and therefore if serum assessments are to be made measurement of the unbound fraction is the method of choice¹⁰⁶. This is especially relevant for those AEDs, such as valproate and phenytoin, that are moderately or highly protein bound.

Several studies have demonstrated pronounced alterations in the pharmacokinetics of lamotrigine during pregnancy^{107–111}. Apparent clearance increases steadily throughout pregnancy, from as early as the 5th week of gestation, peaking at about the 32nd week of gestation, when a 330% increase from baseline has been observed. The observed fall in lamotrigine levels during pregnancy has been reported as being associated with a decline in seizure control compared to preconception baseline in up to 39% of women¹¹². Gestational week has also been found to be a better predictor of lamotrigine clearance than oestradiol concentration. Genetic polymorphism of UGT1A4 and UGT2B7 have a modest role in lamotrigine clearance variation in pregnancy.

Foetal sex may also significantly impact on lamotrigine clearance, with women carrying females having enhanced clearance compared to those carrying males^{113,114}.

Valproate also demonstrates a high degree of dose/concentration variability between different pregnancies (as high as 13- fold). In 33 women who had 51 pregnancies total concentration dose ratios were reduced by almost 50% before pregnancy compared to the third trimester¹¹⁵.

Women with epilepsy followed closely through pregnancy and beyond for 1 year, were assessed with regards to the AED clearances with levetiracetam use (n = 18), oxcarbazepine (n = 4), topiramate (n = 10), valproate (n = 5), and phenytoin (n = 7). Maximal clearance was reached for levetiracetam in the first trimester (1.71 fold), and for oxcarbazepine and topiramate in the second trimester, with 1.63, and 1.39- fold changes in clearance. In this study, lower ratio to target concentrations were associated with seizure exacerbation. The authors advocate early drug monitoring, and dose

adjustment to help reduce increased seizure frequency¹¹⁶. A study of zonisamide in 23 pregnancies in 15 women with epilepsy (6 monotherapy) found the mean serum level fell by over 40%, with a high degree of interindividual variability, but with lowest levels typically in the last trimester. Four of ten seizure free patients had breakthrough seizures¹¹⁷.

There is currently no consensus on how best to monitor AED levels during pregnancy. It has been advocated by the AAN that a baseline, preconception, unbound (free) AED level, repeated at the beginning of each trimester and in the last four weeks of pregnancy should be the minimum level of monitoring. More frequent measurements will be necessary if seizure control deteriorates, side effects ensue, or compliance is an issue. For most AEDs routine monitoring of serum levels is not necessary. For lamotrigine some are of the opinion that close monitoring is mandatory and that drug levels should be increased if serum levels fall, to prevent deterioration in seizure control.¹¹² In a study of 42 women receiving lamotrigine, monthly monitoring, followed by a 20–25% increase in lamotrigine dose, if levels fell below preconception or first trimester baseline was associated with only 19% having an increased seizure frequency¹¹⁸. Whether such practices expose the foetus to additional risk has not however been established. The AntiEpileptic drug Monitoring in PREgnancy (EMPiRE) study is the only double-blind randomised trial assessing the effectiveness and safety of therapeutic drug monitoring during pregnancy in women with epilepsy. No evidence was found to support regular monitoring of AED levels, with there being no improvement in seizure control for those where AED doses were adjusted in response to the results of therapeutic drug monitoring. No differences in foetal outcomes were also observed.¹¹⁹

AED levels quickly revert to pre-pregnancy levels after birth¹⁰⁷. Hence, if the dose of an AED has been increased during pregnancy it may be useful to measure serum levels during the first month after delivery to predict potential toxicity. The decision to reduce the AED dosage if the increase has been made solely because of worsening seizure control during pregnancy should be made on an individual basis. If the increase has resulted in a sustained improvement in seizure control with no evidence of toxicity the dose may be left unchanged.

The effects of epilepsy and in particular seizures on the developing embryo/foetus

The foetus seems relatively resistant to the effects of seizures although anecdotal evidence suggests that tonic-clonic seizures may cause foetal bradycardia¹²⁰ or miscarriage, but definitive data are lacking. There is no evidence that simple partial, complex partial, absence or myoclonic seizures are harmful to the fetus¹²¹. Likewise, prospective studies have not shown an association between tonic-clonic seizures and malformations^{122,123}. Nevertheless, the risk of seizure recurrence, injury, status epilepticus, or even death needs to be considered.

That the effects of status epilepticus in pregnancy were previously felt to be particularly dramatic is well illustrated by Teramo and Hiilesmaa who compiled 29 cases from the literature, of which nine of the mothers and 14 of the fetuses died¹²⁴. In contrast, in the prospective study of seizure control during pregnancy, the EURAP study group did not find such an effect. Of 36 cases of status epilepticus (12 convulsive) there was one stillbirth, but no cases of miscarriage or maternal mortality¹⁰¹. EURAP has however a higher incidence of SE in pregnancy, which requires further investigation¹²⁵.

That women with epilepsy who have seizures during pregnancy may be more likely to have preterm, a small or low birth weight baby compared with women without epilepsy has also been shown in a study from Taiwan¹²⁶. More recent studies of the Danish Medical Birth Registry¹²⁷ and the Medical Birth Registry of Norway¹²⁸ have also observed higher risk of infants with low birth weight (<2500g) or small for gestational age in women with epilepsy who were taking an AED during pregnancy. In both studies this effect was most pronounced in the children of women taking topiramate, with

topiramate also being associated with microcephaly in the Norwegian study. A smaller study from the Oppland Perinatal Database¹²⁹ also found increased risk of infants born to mothers with epilepsy being small for gestational age and having lower ponderal index (kg/m³) compared to controls. This risk was highest for mothers taking carbamazepine and lamotrigine, although the numbers in individual drug groups were small. Only 3 pregnancies exposed to topiramate were included but these had the lowest values for mean head circumference and birth weight in the epilepsy group. Unfortunately, information on seizure control during pregnancy was not included in these studies and remains unclear whether this effect was due to AED consumption or seizures. This effect has also been noted in a recent systematic review and meta-analysis which identified increased risk of preterm birth (37 weeks gestation) O.R. 1.16 CI 1.06–1.34 and foetal growth restriction O.R. 1.26 CI 1.20–1.33¹³⁰. Data from the North American Antiepileptic Drug Pregnancy Registry clarifies that certain AEDs carry a higher risk of a small for gestational age (SGA) outcome, with the highest risks for topiramate, phenobarbital and zonisamide. The relative risk of development of an SGA outcome was 2.0 (95% CI 1.3–3.0) for WWE exposed to AEDs in utero¹³¹.

The effects of AEDs on the developing foetus/embryo

Major congenital malformations

There is albeit largely indirect, evidence from human pregnancies that AEDs have an effect on foetal and embryonic development. It is a consistent finding that women with epilepsy who are not on AEDs have a lower risk of having children with major malformations than those who are taking AEDs¹³². However, whether the two groups are directly comparable is controversial, as women reported as having epilepsy, but who do not require AEDs usually either have very mild epilepsy or epilepsy in remission. It has also been consistently reported that women who take polytherapy are more at risk than those who take monotherapy^{133–135}. Again, this could be argued as simply being a reflection of the severity of the epilepsy. Finally, animal studies have demonstrated teratogenicity with all of the older AEDs¹³⁶.

It is generally accepted that WWE who are taking an AED in monotherapy have at least a 2–3 times increased risk over the background population of having an infant with a MCM (i.e. the risk is 4–9% compared to background of 2–3% for each pregnancy)^{132,133,137,138}.

For AEDs taken in monotherapy, there is a spectrum of risk for individual drugs, with valproate having the greatest risk. There is now also data available for the newer AEDs, with the greatest number of outcomes being reported to date for lamotrigine and levetiracetam¹³⁹.

Regarding the more commonly used drugs in current practice, there have been major changes in the prescribing trends over the last 25 years with the more teratogenic AED agents being prescribed less commonly than the less teratogenic AEDs¹⁴⁰. This has resulted in less valproate being prescribed in younger women, and a preference for lamotrigine and levetiracetam. Carbamazepine has likely become less prescribed due to long term tolerability issues, especially with other efficacious alternatives available. These changes have largely come about due to the knowledge which has been disseminated from several large observational studies (see table 1). The dissemination of this knowledge among clinicians, the embedding of this into various national guidelines, brought about an expectation of a certain standard of care to be delivered to woman with epilepsy during pregnancy. The most commonly used five AEDs in the UK cohort are presented in table 1, along with some other less commonly used AEDs in this cohort of patients. They are presented with their associated MCM frequency, MCM rate across the three major cohort studies.

Despite the temporal trends in prescribing the UK and Ireland Epilepsy and Pregnancy register outcome data for 9247 pregnancies showed a stable percentage of monotherapy to polytherapy

prescribing habits over time. Between 1996 and 2016, the total MCM rate underwent a 2.1% reduction per year (incidence risk ratio 0.979 (95% CIs 0.956 to 1.002) but Poisson regression analysis showed that this was not statistically significant¹⁴¹.

An early case-control study found the rate of major congenital malformations for 210 infants exposed to carbamazepine was approximately twice that in the control group (relative risk 2.24; 95% CI 1.1–4.56)¹⁴². Such an increase was not found by the UK Epilepsy and Pregnancy Register, where the major malformation rate for carbamazepine monotherapy exposures among 1657 prospectively collected pregnancies was 2.6%, with no significant increase in risk from the control group¹⁴³. Carbamazepine has been reported to be associated with major malformations, including neural tube defects, at a rate of anything between 0.2% and 1% of exposed pregnancies¹⁴⁴, with heart defects, inguinal hernia, hypospadias and hip dislocations reported also. There have also been reports of reduced head circumference, weight and length at birth. In a recent systematic review and case control study the EUROCAT Antiepileptic Study Working Group reported that for carbamazepine teratogenicity appeared to be relatively specific to spina bifida¹⁴⁵.

A large US population- based study, using data extracted from Medicaid compared mothers using topiramate (for epilepsy and non-epilepsy indications) and compared to non-exposed pregnancies. A higher relative risk of oral clefts was demonstrated for topiramate use, in epilepsy 8.30 (95% CI 2.65–26.07) compared to those without epilepsy 1.45 (95% CI 0.54–3.86). The risk of oral cleft (at birth) was 4.1 per 1,000 in infants born to women using topiramate, compared with 1.1 per 1,000 in unexposed (RR 2.90, 95% CI 1.56–5.40). A dose response was observed with the relative risk of oral clefts with doses ≤100 mg being 1.64 (95% CI 0.53–5.07) and >100 mg/day was 5.16 (95% CI 1.94–13.73)¹⁴⁶.

Valproate has been shown to increase the risk of major congenital malformations in both preclinical studies and in human pregnancies. That pregnancies exposed to valproate alone have the highest risk for a major congenital malformation has been shown by all the major registry studies. There is also growing data to suggest that total daily dose of valproate is an important determinant for risk of major malformations. Data from all three of the main epilepsy and pregnancy registries has shown a dose-related increase in rates of major congenital malformations with higher valproate doses^{78,143,147}.

While the risks of using valproate in pregnancy are evident it is a very effective drug, particularly for those with generalised epilepsy. The Australian Pregnancy Register¹⁴⁸ identified that stopping valproate therapy before pregnancy was associated with an increased risk of seizures during pregnancy. In generalized epilepsy, this almost doubled the occurrence of seizures from 50% to 100%.

Valproate and the EMA/MHRA (Medicines and Healthcare products Regulatory Agency (MHRA))

A recent publication¹⁴⁹ states new regulatory requirements for valproate use. It demands pregnancy testing prior to commencement of valproate, better provision of information for woman through a formal consent procedure (Risk acknowledgement form) to be completed annually at specialist review, and also the entering a pregnancy prevention programme. Some authors have highlighted the ethical concerns of this approach, limiting choice in women, particularly those who have come to depend on it as an effective treatment of their epilepsy. Furthermore, it is limited in its scope, not considering the issues faced by those for example with marked intellectual disability, where enforcing a contraceptive choice might be considered inappropriate. It is vital to discuss the ongoing risks of the medication in comparison to the risk of deteriorating seizure control^{150,151}.

Table 1. MCM rates for various monotherapy AEDs as well as trends in specific malformations

	Frequency of MCM in reported registries, with associated MCM rate and 95% CI			Spectrum of MCMs ⁽¹³³⁻¹³⁵⁾
	UK and Ireland ^(129, 149)	EURAP ⁽¹²⁵⁾	North American AED pregnancy Registry ⁽¹³²⁾	
Levetiracetam	2/304 (0.70%; 0.2–2.5%)	17/599 (2.8%; 1.7–4.5)	11/450 (2.4%; 1.2–4.3%)	Of 754 exposures: 1 cardiac defect, 1 neural tube defect, 0 cleft abnormalities or hypospadias reported
Lamotrigine	49/2098 (2.3%; 1.8–3.1%)	Dose ≤ 325 mg	46/1870 (2.5%; 1.8–3.3)	Of 7100 exposures: 51 cardiac defects, 7 neural tube defects, 14 cleft palate and cleft disorders, 20 hypospadias
		>325 mg	28/644 (4.3%; 2.9–6.2)	
Valproate	82/1220 (6.7%; 5.5–8.3%)	Dose ≤650mg	38/600 (6.3%; 4.5–8.6)	Of 4270 exposures: 61 cardiac defects, 59 neural tube defects, 31 cleft palate and cleft lip, 56 hypospadias Other features which are reported include : hypertelorism, epicanthic folds, digital hypoplasia, Lower doses correlated with reduced spina bifida and hypospadias
		>650 to ≤1450mg	75/666 (11.3%; 9.0–13.9)	
		>1450 mg	29/115 (25.2%; 17.6–34.2)	
Carbamazepine	43/1657 (2.6%; 1.9–3.5%)	Dose ≤700 mg	58/1276 (4.5%; 3.5–5.8)	Of 7308 exposures: 52 cardiac defects, 21 neural tube defects, 24 cleft abnormalities, 26 hypospadias
		>700mg	49/681 (7.2%; 5.4–9.4)	
Topiramate	3/70 (4.3%; 1.7–13.3%)	6/152 (3.9%; 1.5–8.4)	15/359 (4.2% (2.4–6.8%)	Of 470 exposures: 2 cardiac defects, 6 cleft disorders, 3 hypospadias, 0 neural tube defects
Oxcarbazepine	Not reported	10/333 (3.0%;1.4–5.4)	4/182 (2.2%; 0.6–5.5%)	No clear patterns reported in literature.
Phenobarbital	Not reported	19/294 (6.5%; 4.2–9.9)	11/199 (5.5%; 2.8–9.7%)	Congenital heart defects and facial clefts
Phenytoin	3/82 (3.7%; 1.3–10.2%)	8/125 (6.4%; 2.8–12.2)	12/416 (2.9%; 1.5–5.0)	Congenital heart defects and facial clefts Urogenital defects, and dysmorphic facial and other features such as distal phalangeal hypoplasia

Studies have indicated that exposure to valproate during early pregnancy is associated with a significant incidence (1–2%) of spina bifida aperta^{69,152}, with the greatest risk for those exposed to doses of greater than 1000 mg per day⁷⁰. It has also been reported that there is a greater risk of cardiovascular and urogenital malformations, skeletal defects (including radial ray aplasia and rib and vertebral anomalies^{152–156}), and a combination of facial dysmorphic patterns¹⁵⁷, which is possibly distinct from that seen with other AEDs such as phenytoin. However, the dysmorphic features, such as epicanthal folds, long philtrum, flat nasal bridge, and hypertelorism, occur with other AEDs and their significance for long-term development is unknown. There is evidence of a pharmacogenetic susceptibility to the teratogenic effects of valproate both, from human reports^{158,159} and preclinical studies¹⁶⁰. There is also a suggestion from preclinical studies that for valproate, at least, high peak plasma concentrations are associated with an increased risk of malformations¹⁶¹. This finding was replicated in the Australian study where the mean daily dose of valproate was higher in those with a major malformation¹⁶². Thus, it has been suggested that a sustained-release preparation may be preferable, with the total daily dose being divided into two or three administrations per day. This approach, however, failed to show any benefit in a retrospective analysis by the UK Epilepsy and Pregnancy Register, which showed similar rates of major congenital malformations in women taking standard valproate once daily compared to those taking prolonged-release valproate or standard-release valproate in multiple daily administrations (relative risk 1.1; 95% CI 0.7–1.8)¹⁶³. In January 2015 the MHRA published new and strengthened warnings regarding valproate exposure during pregnancy, advising that, in view of the risk of MCMs and neurodevelopmental delay associated with the drug, it should not be used unless other alternatives are ineffective or not tolerated. It was also advised that valproate should be started and supervised by a clinician with experience in treating epilepsy and that the risks and benefits of treatment should be considered both on commencing valproate and frequently at subsequent reviews, especially when a girl reaches puberty and when pregnancy is being planned¹⁶⁴.

The ILAE¹⁶⁵ have published comprehensive guidance on the use of valproate and the situations where decisions need to be made in relation to valproate, such as the decision to initiate valproate at diagnosis, dealing with valproate in a patient considering pregnancy, and dealing with valproate in a patient who has become pregnant.

EURAP have reported observational data which looked at a group of valproate pregnancies where valproate was either withdrawn (n=93) or switched to an alternative agent (n=38) or maintained (n=1588) in the first trimester. GTCS were twice as common during pregnancy in the withdrawal group (33%) and switch group (29%) compared to the maintained treatment (16%) group. Of the withdrawal group 20% had to restart valproate later in pregnancy or else an alternative agent¹⁶⁶.

Considering the newer AEDs, most human data are available for lamotrigine. The International Lamotrigine Pregnancy Registry has recently reported the outcomes of 1558 first trimester lamotrigine-exposed pregnancies¹³⁹. The percentage of outcomes exposed to lamotrigine monotherapy with major birth defects was 2.2% (95% CI 1.6–3.1%). For polytherapy outcomes containing lamotrigine the occurrence of birth defects varied according to whether sodium valproate was included in the polytherapy regimen. For combinations containing sodium valproate in addition to lamotrigine (n = 150) the rate of major birth defects was 10.7% (95% CI 6.4–17.0%). This compared with a rate of 2.8% (95% CI 1.5–5.0%) for polytherapy combinations which included lamotrigine but not sodium valproate (n = 430). No distinctive pattern of malformations was reported in this study. Data from the UK Epilepsy and Pregnancy Register revealed a similar malformation rate for pregnancies exposed to lamotrigine alone, with 49 of 2098 (2.3%) infants having a major congenital malformation. In contrast to earlier results, only a small dose-response was seen with 3.4% of pregnancies exposed to more than 400 mg a day of lamotrigine having a major congenital malformation, compared to 2.1% of those exposed to less than 200mg daily¹⁴³. This did not reach

statistical significance. A positive dose-response has not been reported by some other registers including the International Lamotrigine Registry¹³⁹. The North American Pregnancy Register reported a total of 31 (2.0%) of 1562 infants exposed to lamotrigine to have a major congenital malformation. No dose response was found but a 10.4-fold (95% C.I. 4.3–24.9) increase in the rate of clefting abnormalities was noted¹⁶⁷. In contrast the UK Epilepsy and Pregnancy Register^{143,168} and the European Surveillance of Congenital Anomalies found no evidence of increased isolated orofacial clefts relative to other major congenital malformations for lamotrigine¹⁶⁹.

Reported data on the other new AEDs are sparse. The North American AED Pregnancy Registry has reported an MCM rate for oxcarbazepine as 2.2% [4/182]¹⁴⁷ with EURAP reporting similar figures 3.3% [6/184]⁷⁸. Another report of 55 exposures to oxcarbazepine (35 monotherapy and 20 polytherapy) noted only one major malformation¹⁷⁰. Six malformations from the outcomes of the 248 monotherapy exposures to oxcarbazepine (2.4%), either reported in the literature or held by the Novartis Germany database, have also been reported¹⁷¹.

In a post-marketing surveillance study of gabapentin as add-on therapy for 3100 patients in England no congenital abnormalities were seen in the 11 infants born to women who used gabapentin in the first trimester of pregnancy¹⁷².

In the tiagabine clinical trials 22 patients who received the drug became pregnant, of whom nine carried to term. In one of these a hip displacement was noted, though this was a breech delivery¹⁷³.

Preliminary data for topiramate appears concerning. The UK Epilepsy and Pregnancy Register reported on 203 pregnancies exposed to topiramate. (4.3%) had a major congenital malformation [3/70 cases], of which two were clefting abnormalities and one a case of hypospadias¹⁷⁴. Results from the North American AED Pregnancy Registry (15 from 359 pregnancies, 4.2%)¹⁴⁷ and EURAP (five from 73 pregnancies, 6.8%)⁷⁸ were similarly concerning, and in 2011 topiramate was reclassified as a category D drug by the FDA to reflect these results. Earlier results published by the North American AED Pregnancy Registry in abstract form were in keeping with results from the UK Epilepsy and Pregnancy Register, with two of eight major congenital malformations from 197 exposures to topiramate being cleft lip deformities¹⁵⁵. More recent population-based studies from Norway¹²⁷ and Denmark¹²⁸ have also suggested an association between topiramate exposure in pregnancy and foetal growth restriction, infants being born small for gestational age and microcephaly.

Increasing data is now available for levetiracetam. The UK Epilepsy and Pregnancy Register reported a 0.7% risk of major malformations from 304 pregnancies exposed to levetiracetam in monotherapy¹⁷⁶. Similarly reassuring results have also been published by the North American AED Pregnancy Registry (11 from 450 pregnancies, 2.4%)¹⁴⁷ and EURAP (two from 126 pregnancies, 1.6%)⁷⁸. Collation of many more pregnancies would clearly be beneficial to clarify the safety of these AEDs in pregnancy.

For zonisamide data for exposed pregnancies is limited. Animal and early human studies previously raised concerns regarding use of zonisamide during pregnancy. However, data recently published by the North American AED Pregnancy Registry is less concerning, with no malformations observed among 90 monotherapy-exposed pregnancies (95% CI 0–3.3)¹⁴⁷. Study of much larger numbers of pregnancies is required to confirm the validity of these findings.

For all the newer AEDs, preclinical models are therefore of interest. In these studies, topiramate was teratogenic in mice, rats and rabbits at high doses, with limb and digital malformations, including right-sided ectrodactyly being observed in rats and rib and vertebral malformations in rabbits. Vigabatrin was also shown to be teratogenic in rabbits, inducing cleft defects¹⁷⁷. Gabapentin

was associated with skeletal malformations, including delayed ossification of the calcaneus and hind limb digits in mice, and incomplete fusion of skull bones and sternabrae in rats. However, the type and incidence of these abnormalities were not felt to be indicative of developmental toxicity¹⁷⁸. Tiagabine, oxcarbazepine and levetiracetam have not been shown to be teratogenic. Animal models of the neurodevelopmental effects of AED have suggested AED induced apoptosis, changes in the neurotransmitters and effects on synaptogenesis as putative mechanisms explaining neurodevelopmental delay in rodent and primate animal models¹⁷⁹.

When considering the effect of AEDs on embryonic and foetal development, most of the emphasis to date has been on the risk of major congenital malformations. However, there is good evidence that minor anomalies, learning difficulties and other problems may also be related to AED therapy. It has been found that the children of women with epilepsy, whether or not they are taking AEDs, are at increased risk of minor anomalies¹⁸⁰, and specific AED-related fetal syndromes have been suggested for most of the older AEDs^{169,157,181}. The types of abnormalities found have included minor craniofacial and digital anomalies and growth retardation. However, possibly except for valproate^{157,182}, there is no real convincing evidence that specific syndromes are associated with specific AEDs, hence the term 'foetal-AED' syndrome may be more appropriate. It is unclear what the influence of other variables is, such as maternal epilepsy and hereditary factors. In any case such abnormalities, although undesirable, have usually been felt in themselves to cause little disability. However, whether or not they are markers for more diffuse problems, cognitive and behavioural upset is increasingly being questioned in particular.

Neurodevelopmental outcomes

The effects of AEDs on long-term cognitive functioning of children exposed to AEDs in utero have not been studied as extensively as major congenital malformations, and of the studies completed methodological issues have limited interpretation¹⁸³. While previous studies have shown mean IQ to be significantly lower in the children of women with epilepsy^{87,184,185} it was suggested that this is independent of AED exposure. However, a growing number of retrospective and prospective studies have found that developmental delay is more common in children born to mothers or fathers with epilepsy. There is also an increasing body of evidence to suggest that these effects vary by AED exposure, with valproate consistently being associated with poorer outcomes, which are likely to persist long term. One early study found that 16% of 224 children who had been exposed to AEDs prenatally had additional educational needs compared with 11% of 176 exposed to no drugs (odds ratio 1.49; 95% CI 0.83–2.67%)¹⁸⁶. A total of 30% of those exposed to valproate, and 20% exposed to polytherapy containing valproate, had additional educational needs. This compared with 3.2% and 6.5% exposed to carbamazepine and other monotherapy regimes, respectively. In a more thorough investigation of partly the same cohort of children the authors found that verbal IQ was significantly lower in children exposed to valproate monotherapy (mean 83.6; 95% CI 78.2–89.0%; n = 41) than in unexposed children (90.9; CI 87.2–94.6%; n = 80) or in children exposed to carbamazepine (94.1; CI 89.6–98.5; n = 52) or phenytoin (98.5; CI 90.6–106.4; n = 21). Multiple regression analysis revealed exposure to valproate, five or more tonic-clonic seizures in pregnancy and low maternal IQ to be associated with lower verbal IQ after adjustment for confounding factors. Doses of valproate above 800 mg/day were associated with lower verbal IQ than lower doses. There was also a significant negative correlation between dysmorphic features and verbal IQ in children exposed to valproate¹⁸⁷. These results compare with those from previous studies which have shown higher rates for developmental delay for infants exposed prenatally to carbamazepine of between 8% and 20%^{183,188,189}. In another study 24% of AED exposed infants had a developmental disorder compared with 10.5% of non-exposed siblings. Differences were noted between AEDs. However, infants exposed to carbamazepine, phenytoin and valproate had significantly higher rates of developmental delay than infants not exposed to AEDs¹⁹⁰.

In a study from Finland the authors reported similar findings among a small number of exposed infants where full-scale IQ was low (<80) in four of 21 infants that had been exposed to valproate (19%) and exceptionally low (<70) in two infants (10%). Of importance however, the mothers of the valproate exposed group performed significantly worse on IQ tests and also had significantly lower educational levels¹⁹¹.

A later study from India addressed some of the above concerns. Using an Indian adaptation of the Bayley Scale of Infant Development, motor and mental development were measured in 395 infants born to women with epilepsy¹⁹². In addition to paediatricians being blinded to AED exposure, multiple confounders were taken into account. Unfortunately, these did not include maternal IQ. Valproate was associated with significantly lower mental and motor developmental scores, compared with carbamazepine, but not with other AEDs used in monotherapy. While maternal educational status was significantly correlated with motor development in infants, mental development was not. The importance of including all confounding variables was shown in a prior study from the same group where low maternal IQ and maternal education as well as AED exposure were found to be associated with significant impairment of intellectual and language functions in children of mothers with epilepsy¹⁹³.

The situation for the newer AEDs is even less clear, with very limited data being available on their influence on cognitive functioning and other aspects of development. With regard to lamotrigine data to date suggests less of a deleterious effect on neurocognitive development than for valproate. The Neurodevelopmental Effects of Antiepileptic drugs (NEAD) study assessed IQ and multiple other cognitive domains in children at six years of age. Mean IQ in the valproate group was reduced by 11 points compared with the lamotrigine group, 11 points compared with the phenytoin group and 8 points compared with the carbamazepine group⁸¹. The association between valproate use and IQ was dose dependent. Fetal valproate exposure was also significantly associated with a wide range of cognitive deficits, including reduced measures of verbal ability, non-verbal ability, memory and executive function that were also dose-related. Children's IQs were significantly related to maternal IQs among children exposed to carbamazepine, lamotrigine and phenytoin but not among those exposed to valproate. That valproate is associated with worse cognitive outcomes compared with lamotrigine and carbamazepine, in particular with regard to language skills, has also recently been reported by other authors¹⁹⁴⁻⁷. A Cochrane review published in 2014 included 22 prospective cohort studies and 6 registry based studies. It concluded that the IQ of children exposed to valproate during pregnancy was lower than those of women without epilepsy or with untreated epilepsy. IQ for children exposed to valproate was on average 8.69 points lower than those exposed to carbamazepine, 10.8 points lower than those exposed to lamotrigine and 9.25 points lower compared to phenytoin, with a dose effect being reported in 6 studies. The magnitude of these results was felt to be sufficient to affect educational and occupational outcomes later in life. No significant association was found between carbamazepine exposure and development quotient or IQ¹⁹⁸.

Recent data published by the Liverpool and Manchester Neurodevelopment Group suggests that there may also an association between AED use during pregnancy and other neurodevelopmental disorders such as Asperger's syndrome, ADHD, autistic spectrum disorders (ASD) and dyspraxia. Neurodevelopmental disorders were more frequently seen in the children of women with epilepsy (15 of 201, 7.46%) compared to control women (four of 214, 1.87%). Although the numbers in each group were small, a differential effect of AED exposure was seen, with valproate exposure being associated with an odds ratio for neurodevelopmental disorders of 6.05 compared to the control group (P = 0.007). Lamotrigine was also associated with a higher incidence of neurodevelopmental disorders than the control group (6.67%, odds ratio 4.06), but this was not statistically significant (P = 0.1)¹⁹⁹.

Similar results were described in a recent population-based study from Denmark, which also found a higher incidence of ASD and childhood autism in children exposed to valproate during pregnancy. In this study, from all children born alive in Denmark from 1996 to 2006 (total 665,615) 5437 children were identified with ASD, including 2067 with childhood autism. In this population, 2644 were exposed to AEDs during pregnancy and 508 were exposed to valproate. In women with epilepsy, the use of valproate during pregnancy was associated with an increased absolute risk for ASD (4.15%; 95% CI 2.20–7.81%) and childhood autism (2.95%; 95% CI 1.42–6.11%) compared to those exposed to other AEDs (2.44%; 95% CI 1.88–3.16% and 1.02%; 95% CI 0.70–1.49% respectively). Exposure to carbamazepine, lamotrigine, oxcarbazepine or clonazepam was not associated with a significantly higher risk for these disorders²⁰⁰.

Data for the other newer AEDs are restricted mainly to levetiracetam. Studies from the Liverpool and Manchester Neurodevelopmental Group and the UK Epilepsy and Pregnancy Register, which compared cognitive development up to 3 years of age in children exposed to levetiracetam and valproate, children exposed to levetiracetam in utero (n=53) were not at an increased risk of delayed early development compared with control children. In contrast those exposed to valproate scored significantly worse²⁰¹. The fact that levetiracetam doesn't appear to result in cognitive delay was also recognised when a group of school age children exposed to in utero levetiracetam (n=42) were assessed for IQ, memory, language, and attention in comparison to controls and were found to be comparable²⁰². Studies on the neurodevelopment of children exposed to topiramate are limited, with one uncontrolled study which assessed 9 children finding poorer IQ and cognitive skills. A more recent and larger report did not find any significant difference in the IQ, memory, language or attention of 27 topiramate exposed children compared to controls, and levetiracetam²⁰². Longer term follow-up of these cohorts is required as the numbers are currently too small to give reassurance²⁰³.

Management of labour and postpartum management of mother and child

During Labour

Most women with epilepsy will have a normal uncomplicated vaginal delivery⁸⁴. However, in approximately 2–4% the stress of labour may result in an increased risk of seizures during labour or in the following 24 hours^{133,204}. Tonic-clonic seizures may result in foetal hypoxia and it is therefore generally recommended that delivery takes place in a unit equipped with facilities for maternal and neonatal resuscitation^{98,99}. Meta-analysis showed WWE compared to controls had higher risk of antepartum (OR 1.49 CI 1.09–2.20) and postpartum haemorrhage (1.29 CI 1.13–1.49), hypertensive disorders (1.37 CI 1.21–1.55), induction of labour (1.67 CI 1.31–2.11), caesarean section (1.40 CI 1.23–1.58), Risk of perinatal death and admission to neonatal ICU didn't differ¹³⁰. In a cohort study from Norway, being overweight prior to pregnancy in WWE has a strong negative effect on the risk of complications of delivery and pregnancy²⁰⁵.

Breastfeeding

WWE are less likely to breastfeed than their counterparts without epilepsy according to a retrospective survey of postpartum women in the US (Pregnancy Risk Assessment Monitoring System²⁰⁶. It is generally encouraged and may even have the additional advantage of gradually weaning the infant from the AED²⁰⁷. AEDs are secreted in breast milk inversely proportional to the level of maternal serum protein binding, resulting in varying exposures in breast milk with different AEDs. Other factors which impact on this include concentrations of AEDs which can differ substantially between the start and end of a meal, and between the right and left breast depending on the fat and protein contents of the milk. Lipid soluble AEDs are found in breastmilk,

but not typically at levels which can cause side effects. Barbiturates, benzodiazepines, lamotrigine, zonisamide, and ethosuximide can be increased and result in lethargy and irritability²⁰⁷. For some AEDs, such as phenobarbitone and primidone, reduced neonatal serum protein binding and immature elimination mechanisms can also result in drug accumulation. This can result in sedation of the infant and necessitate the discontinuation of breastfeeding. However, for most AEDs including phenytoin, carbamazepine and valproate,²⁰⁸ breastfeeding is usually without problems as these drugs are highly protein bound and poorly excreted into breast milk. One interesting case report found high carbamazepine levels in breast milk and the mothers serum, in the context of the infant (40 day old) having intractable vomiting reversible on discontinuation of breast feeding²⁰⁹. Information on the concentration in breast milk of the newer AEDs is rather limited as yet²¹⁰, however preliminary data indicate that lamotrigine passes into breast milk at 40–45% of the level in plasma, with levels comparable to those seen in patients having been noted²¹¹. For levetiracetam, plasma concentrations in breastfed infants are low despite extensive transfer of levetiracetam into breast milk²¹². Women should be alert to the signs that the neonate is receiving too high a level of AEDs in the milk.

The NEAD study provides reassuring data with respect to the cognitive development of infants exposed to AEDs in breastmilk, albeit in only 181 children receiving phenytoin, carbamazepine, valproate or lamotrigine. At age 6 years, breastfed children had higher IQ and enhanced verbal and non-verbal memory and executive functioning compared to non-breastfed infants. There was no evidence of an adverse effect on cognitive development either for all AEDs combined or for those exposed to the individual AEDs studied (phenytoin, carbamazepine, lamotrigine or valproate)²¹³.

Risk of injury

Risk of injury to the infant largely depends on seizure type and frequency. Any such risk can be minimised if time is allocated to training mothers with epilepsy on safe handling, bathing techniques, breast-feeding, and safe practice around the home.

Pregnancy and Mortality risk

A recent retrospective cohort study from the United States highlighted the elevated risk of mortality during the delivery hospitalisation, finding a >10 fold increased risk of death in pregnant mothers (80/100,000 pregnancies compared to controls without epilepsy 6/100,000 pregnancies). The study was limited as cause of death was not determined²¹⁴. The latest MBRRACE-UK confidential enquiry report²¹⁵ assessing maternal deaths in WWE found 14 maternal deaths between 2009–2012, of which twelve were due to sudden unexpected death in Epilepsy (SUDEP) and two from drowning. Key areas highlighted for improvement were the need for robust pre-conceptual counselling, involvement of an epilepsy specialist, and ideally improved control prior to pregnancy. Case-control level evidence has identified drug choice may affect risk of SUDEP, with a Norwegian study²¹⁶ showing in 26 cases of SUDEP that lamotrigine was associated with an increased risk, perhaps due to falling serum levels and increased seizures in later pregnancy. Data from a Danish Central registry have provided more reassuring risk estimates with regards to death in women with epilepsy in pregnancy. Over 2 million pregnancies were identified, and of these 0.57% (11,976) were in mothers with epilepsy. In total 176 maternal deaths occurred, with 5 of these in women with epilepsy. [41.7 deaths per 100,000 pregnancies in women with epilepsy, compared to 8.2 deaths per 100,000 pregnancies in women without epilepsy]. This resulted in a >5- fold increase in risk of death for women with epilepsy²¹⁷.

Epilepsy and the menopause

The effects of epilepsy on the menopause and the effects of the hormonal changes of the menopause on epilepsy cannot be reliably predicted.

On average menopause occurs at age 51 years of age (or within a range between 42–58 years). WWE tend to enter menopause 2–3 years earlier with higher seizure frequency appearing to be predictive of this²¹⁸, with a consequent reduced fertile window.

Despite the fact there is experimental evidence that oestrogen is a potent proconvulsant and progesterone has anticonvulsant properties and the fact that the peri-menopausal years brings a gradual rise in the oestrogen to progesterone ratio, the menopause appears to have a limited impact on seizure frequency, unless the woman has a history of catamenial epilepsy where this appears more relevant and they may experience a decrease after menopause is complete²¹⁹.

A small RCT²²⁰ has been completed looking at the effect of HRT on seizure frequency in post-menopausal women, although is limited by the fact that it only looked at short term HRT and one particular type (CEE/MPA – conjugated equine oestrogens/medroxyprogesterone acetate). It is not yet clear if other types of HRT could be considered or would be beneficial for seizure frequency. Consideration should be made also to dosage of HRT if there is concomitant use of enzyme inducing AEDs²³.

Women with epilepsy are at increased risk of bone demineralisation, especially if they are receiving a hepatic enzyme-inducing AED (phenobarbitone, phenytoin, and carbamazepine), which can accelerate vitamin D metabolism^{221,222}. This problem may not be restricted to enzyme inducing AEDs, and there are some suggestions valproate may also affect bone health²²³. More prospective studies are required to inform us in this area.

Both seizures and AEDs affect the hypothalamic-pituitary-adrenal axis, which can have an adverse impact on bone health. No assessment has been made on the optimal frequency with which women on long-term AEDs should have bone density monitored. In the general population, hormone replacement therapy (combined oestrogen and progesterone) appears to have beneficial effects in postmenopausal women and it should be offered to postmenopausal women with epilepsy if it is clinically indicated²²⁴.

AEDs and physical appearance

Phenytoin therapy in childhood can lead to hirsutism, gingival hyperplasia and coarsening of facial features. Sodium valproate can cause hair loss, acne and hirsutism. Sodium valproate can stimulate appetite leading to obesity, as can vigabatrin, gabapentin and pregabalin.

Conversely, topiramate can cause significant and even undesirable weight loss. The occurrence of these side effects can have a particularly detrimental psychological effect during adolescence, potentially resulting in reduced compliance with AED therapy.

Psychiatric issues during and after Pregnancy

Depression and anxiety²²⁵ are important issues for those with epilepsy, including WWE, who are prone to peripartum and postpartum exacerbations of psychiatric conditions. One questionnaire study²²⁶ in WWE found that those with epilepsy were less likely to receive treatment compared to controls who were healthy. Pre-pregnancy psychiatric issues, and a history of abuse are risk factors for poor psychiatric recovery. Breastfeeding issues²²⁷ can affect maternal mood, and clinicians should ask about this at post-partum review.

Concerns regarding²²⁸ the impact of anti-depressants resulting in major congenital malformations, neurodevelopmental issues, and low birth weight have been reported, but it is not yet clear to what

extent anti-depressants can result in these outcomes. In a relatively small study from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy²²⁹ they did not find added teratogenic risk in 88 WWE using antidepressant drugs (including SSRI and SNRIs) and AEDs (MCM 9/88; 10.2%; 95% CI 3.9–16.6) when compared to those not receiving anti-depressant drugs. Antidepressant drugs did not appear to worsen seizure frequency or cause altered fetal birthweight. Given the risk of adverse psychiatric outcomes, and its consequent impact on quality of life, it is an area where clinicians should remain vigilant. Suicide risk assessment should also be carried out by epilepsy specialists, given its three fold increase in those with epilepsy, and having urgent referral pathways in place for those where psychiatric input is required²³⁰.

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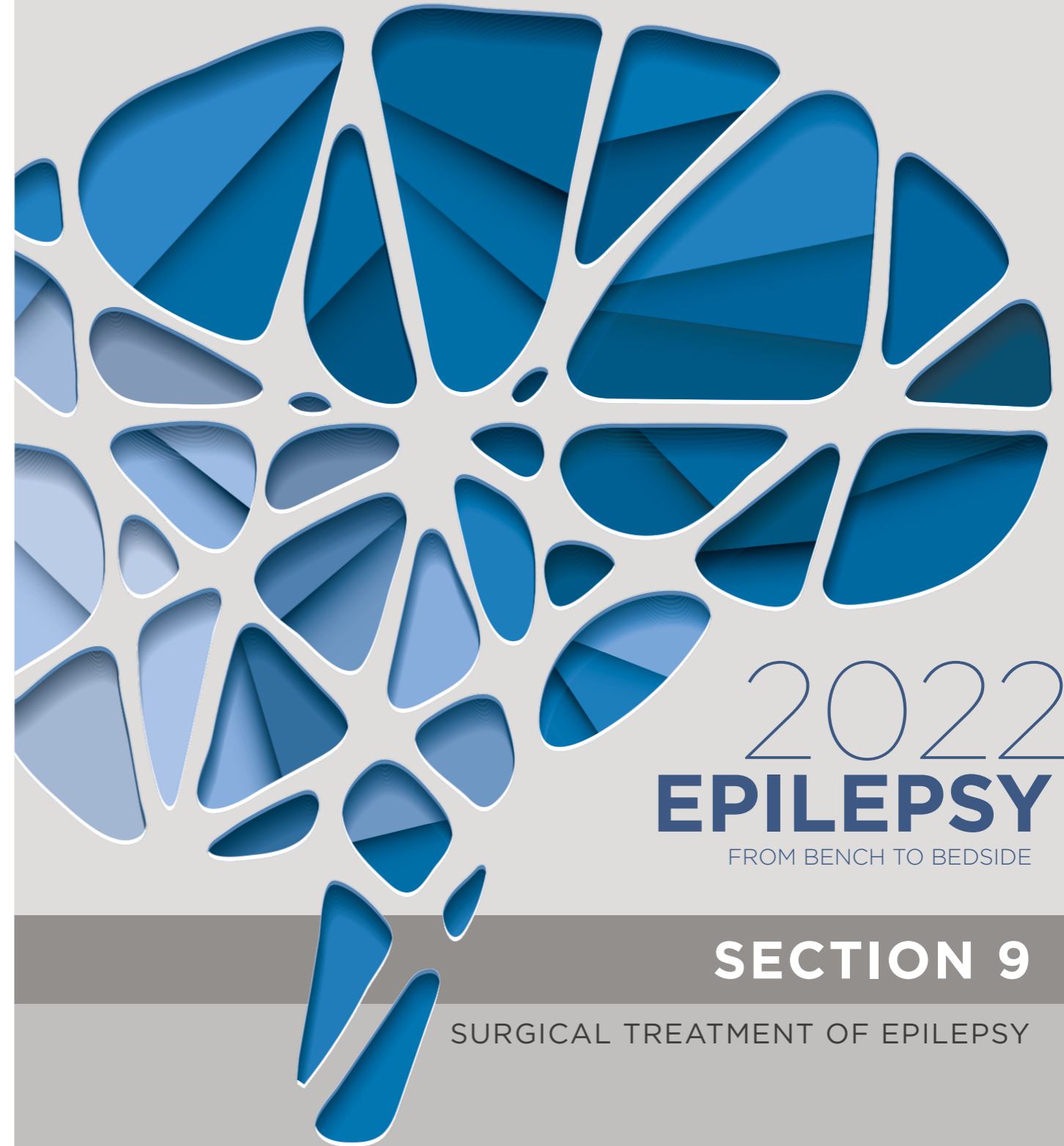
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2022
EPILEPSY
 FROM BENCH TO BEDSIDE

SECTION 9

SURGICAL TREATMENT OF EPILEPSY

CHAPTER 46

Pre-operative evaluation and outcome of surgical treatment of epilepsy

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It has been estimated that there are approximately 750-1500 new cases per annum in the UK who could benefit from epilepsy surgery, and who thus require presurgical assessment. Others may require surgery regardless of seizure control for removal of a progressive lesion (e.g. tumour) or a lesion that has other inherent risks such as danger of haemorrhage (e.g. arteriovenous malformation).

The purpose of pre-operative evaluation is three-fold:

- 1) to assess the potential for operative success
- 2) to identify the most suitable type of operation
- 3) to assess the risk-benefits of such an operation.

Patient selection

The principles for patient selection are:

Drug resistant seizures. Before someone can be considered drug resistant, there has to be an adequate trial of therapy; there is, however, some debate as to what constitutes an adequate trial of therapy. Most centres would consider treatment with at least two first-line antiepileptic drugs (AEDs) appropriate to the type of epilepsy over a period of two years. This is because the chance of a patient becoming seizure free diminishes if control is not achieved with initial therapies, and evaluation for surgery should not be delayed while every possible combination of medication is tried.

Seizure frequency and severity such as to cause significant social and medical disability. It is again difficult to be proscriptive here, and each case needs to be discussed on an individual basis. It is important to remember that there is not only an associated morbidity attached to seizures, but also an associated mortality (including sudden unexpected death, or SUDEP) that may be higher than 1% per annum for the type of patients undergoing pre-surgical assessment.

Reducing or stopping the seizures would result in a significant improvement in quality of life. Severe learning difficulties and psychiatric disease are relative contraindications, as seizures may constitute a minor part of the person's disability. Furthermore there has to be a realistic view of the possible benefits by both patient and carers. Careful counselling to assess and to inform patient expectations is necessary before surgery.

Convergent data from different investigative modalities localise the epileptogenic zone. This is important for curative epilepsy surgery (see below), but is of lesser importance for palliative surgery such as corpus callosotomy and vagal nerve stimulation.

Acceptable risk-benefit ratio benefit for surgery. Even though there may be a high chance of seizure freedom, the risks of operation may be unacceptable (e.g. removal of dominant temporal lobe may result in unacceptable memory deficits even if seizures are halted). The longer-term consequences of seizures (especially in children and adolescents) have to be weighed against the immediate risks of operation. When such an assessment has been made, it is important that the patient is fully informed and is clear about the possible risks and benefits (this requires careful pre-operative counselling).

Presurgical evaluation

Assessment for surgery involves a multidisciplinary approach including: neurologist, neurosurgeon, psychologist, psychiatrist, neurophysiologist and radiologist. There are two main strategies for the surgical treatment of seizures. The first involves resective surgery, in which the aim of the surgery is the removal of the epileptic focus itself. Examples of this type of surgery are anterior temporal lobectomy, selective amygdalohippocampectomy (in which only the mesial temporal structures are removed), or resection of a specific lesion. At the other extreme of resective surgery is hemispherectomy, suitable for patients in whom most or all of one hemisphere is abnormal. The other strategy for surgical treatment is palliative, either to interrupt the pathways of seizure spread (e.g. corpus callosotomy and multiple subpial transection) or to reduce brain excitability (e.g. vagal nerve stimulation).

For curative resective surgery, it is imperative to identify the epileptogenic zone. Congruence is thus sought between the results of the following investigations:

- Clinical history and seizure pattern (seizure semiology)
- Neuropsychometry
- Neuroimaging (high resolution MRI with thin T1-weighted sections, T2-weighted sequences, proton density sequences, and FLAIR sequences)
- Scalp EEG (ictal onset, inter-ictal abnormalities).

Other investigative techniques (e.g. magnetoencephalography, ictal SPECT, PET) are useful in selected cases.

These results are interdependent, and thus, for example, the numbers of seizures that need to be recorded on video-EEG telemetry will vary according to the results of the neuroimaging and type of epilepsy. Indeed, in some patients, in whom there is strong concordance of inter-ictal abnormalities with other investigative modalities, video-EEG telemetry may be unnecessary.

Discordance amongst these investigations reduces the chance of a good outcome. The relative weighting for each of these investigations has yet to be established, but it is clear that neuroimaging revealing the underlying pathology is of high significance. Intracranial EEG monitoring with subdural electrodes and/or depth electrodes may be required in cases of discordance or to localise accurately the epileptogenic zone. In addition, intracranial stimulation either during awake craniotomy or extra-operatively with chronic intracranial electrodes may be necessary to define the safe margins of resection.

Patient history can also give information that may inform the odds of success, including patient age, age of epilepsy onset, epilepsy duration, the occurrence of secondary generalised seizures and status epilepticus and antecedent history, including the presence of head injuries, meningitis or febrile seizures.

Pre-operative assessment is also used to determine the possible risks of operation. These will depend upon the site of operation, the pathology and the type of operation. Psychiatric assessment prior to surgery is mandatory in order to document evidence of psychiatric morbidity prior to surgery, determine adequacy of consent, identify treatable psychiatric conditions that may require separate interventions and to flag up patients who may need additional psychiatric support peri- and post-operatively.

Neuropsychological assessment is also used to estimate the psychological sequelae of epilepsy surgery. This is frequently used to estimate the possible deterioration in memory that will occur with temporal lobe resection. The use of the intracarotid sodium amytal test in patients undergoing temporal lobe resection is diminishing, because of concerns about its accuracy and usefulness in predicting memory decline following surgery. At the National Hospital for Neurology and Neurosurgery, we have abandoned this test. It is still used in some centres, however, to test patients in whom there is discordance between neuropsychometric testing and neuroimaging and in whom an operation is thought to have a reasonable chance of success. fMRI is increasingly being used to lateralise language function, and may in the future also be used to help with memory lateralisation.

Details of risk-benefit discussions with the patient and family need to be recorded in the patient notes and given to the patient in writing. This information should include an estimate of the chances of operative success, along with the risks of complications from the operation (including the risks of permanent neurological sequelae) and the impact that these will have on the patient's lifestyle. Information on the potential psychiatric and psychological sequelae also needs to be given. Pre- and peri-operative counselling is crucial for all patients undergoing epilepsy neurosurgery.

Further reading

SHORVON S, PERUCCA E, ENGEL J *et al* (2016) *Treatment of Epilepsy* (4th Edition). Wiley-Blackwell, Oxford.

CHAPTER 47

Presurgical evaluation and outcome of epilepsy surgery in childhood

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Introduction

Surgery in the management of children with epilepsy is not new. Murray Falconer, a neurosurgeon at the Maudsley Hospital, recognised that children as well as adults may benefit from resective surgery, but the age range of his patients did not include the very young¹. Traditionally, focal seizures have been more difficult to diagnose in the young child, both clinically and electrographically, and a focal onset to seizures may not be readily apparent. However, the advent of magnetic resonance imaging (MRI), with the increased detection of structural focal brain abnormality, has opened up the possibility of surgery at an earlier stage in the natural history of childhood epilepsy.

Selection criteria

There are several points to discuss when considering whether surgery may be more beneficial earlier rather than later. Many adults presenting for resective surgery have a history of seizures arising from early childhood, and have been through multiple antiepileptic drugs (AEDs). Prior to the recognition of different types of epilepsy there was concern that children may 'grow out' of epilepsy but with the use of the classification of the epilepsies the syndromes with a relatively good prognosis can now be recognised at an early stage, and when these have been excluded the focal epilepsies are among the most drug resistant. Chronic epilepsy is not without psychosocial morbidity however; the Oxford study of 100 children with temporal lobe epilepsy demonstrated that at least one-third were not leading an independent life in adulthood². Early surgery may, therefore, reduce the morbidity associated with frequent seizures through the teenage years.

There are specific issues related to children that need to be considered in the discussion of the early surgical treatment of epilepsy. The definition of 'medically intractable epilepsy' in adult practice is often defined as epilepsy which has not responded to at least three AEDs over at least a three-year period. Although in the older child attending normal school this may have relevance, in the young child experiencing recurrent seizures, and where compromise to developmental progress has been demonstrated, it is likely that a greater number of drugs will have been tried over a lesser period of time. Perhaps the most appropriate definition of intractability in children is 'inadequate seizure control in spite of appropriate medical therapy' with no particular timescale. This has been addressed in the recent ILAE report on drug resistance, where drug-resistant epilepsy is now defined as 'a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom'³.

The whole issue of what is 'intractability' in childhood remains a question for debate and we lack tools for prediction of prognosis. We know from epidemiological studies that poor prognostic indicators are early onset of seizures, poor response to first-line medication, focal seizures, and a demonstrable structural lesion. Therefore, we can only assume that with early cessation of seizures

we allow the child to achieve its optimal learning potential. Longitudinal studies post surgery have been lacking, not least because of a lack of standardised tools to assess cognitive performance across all ages. However, at the very least, children have been demonstrated to maintain their developmental trajectory post surgery that would otherwise have been lost, and recent data looking at children who have undergone early surgery suggests improved developmental outcome may be achieved⁴. More recent data suggest greater benefits may be achieved in the longer term, with studies demonstrating greater developmental gains in seizure-free patients the longer duration of time following surgery^{5,6}.

The group of children for whom surgery is considered is also more diverse than the adult group. A significant number will have developmental compromise, in whom an improved quality of life is a priority rather than solely freedom from seizures (although this is obviously a consideration). Assessment for surgery should, therefore, be in the context of a complex epilepsy service⁷. The need for concentration of resources required for epilepsy surgery in children has been recognised in England and Wales with the designation of four nationally funded centres as part of the Children's Epilepsy Surgery Service (CESS) since 2012.

Types of surgery

The types of surgery performed in children do not differ a great deal from those in adults, but the proportion of each procedure carried out, and the type of patient on which it is performed, both vary. An international survey of 458 operations performed in 450 children over a 12-month period (2004) revealed two-thirds (63%) to be hemispherectomy or multilobar resections (Figure 1). Unilobar resections or lesionectomies were undertaken in 30%, with only a very small number of functional procedures being performed⁸. Furthermore, 63% were due to underlying developmental as opposed to acquired pathology⁹.

Focal resection involves removal of a small part or the whole of one lobe. Seizures should be shown to arise from one area of the brain, the removal of which will not interfere significantly with function. Hemispherectomy is considered in children with a pre-existent hemiparesis (in the absence of progressive disease) with a demonstrable structural abnormality of the contralateral hemisphere. In a small number of children with Rasmussen's syndrome (chronic encephalitis involving one cerebral hemisphere) surgery may be considered prior to the development of a dense hemiparesis. This may also be considered in children with Sturge-Weber syndrome with early onset seizures and recurrent status epilepticus.

Corpus callosotomy is considered in children with 'drop' attacks, whatever the seizure type (e.g. akinetic, myoclonic, tonic). This procedure is unlikely to have any effect on other seizure types, and a child is highly unlikely to be rendered seizure free by the procedure.

Figure 1A

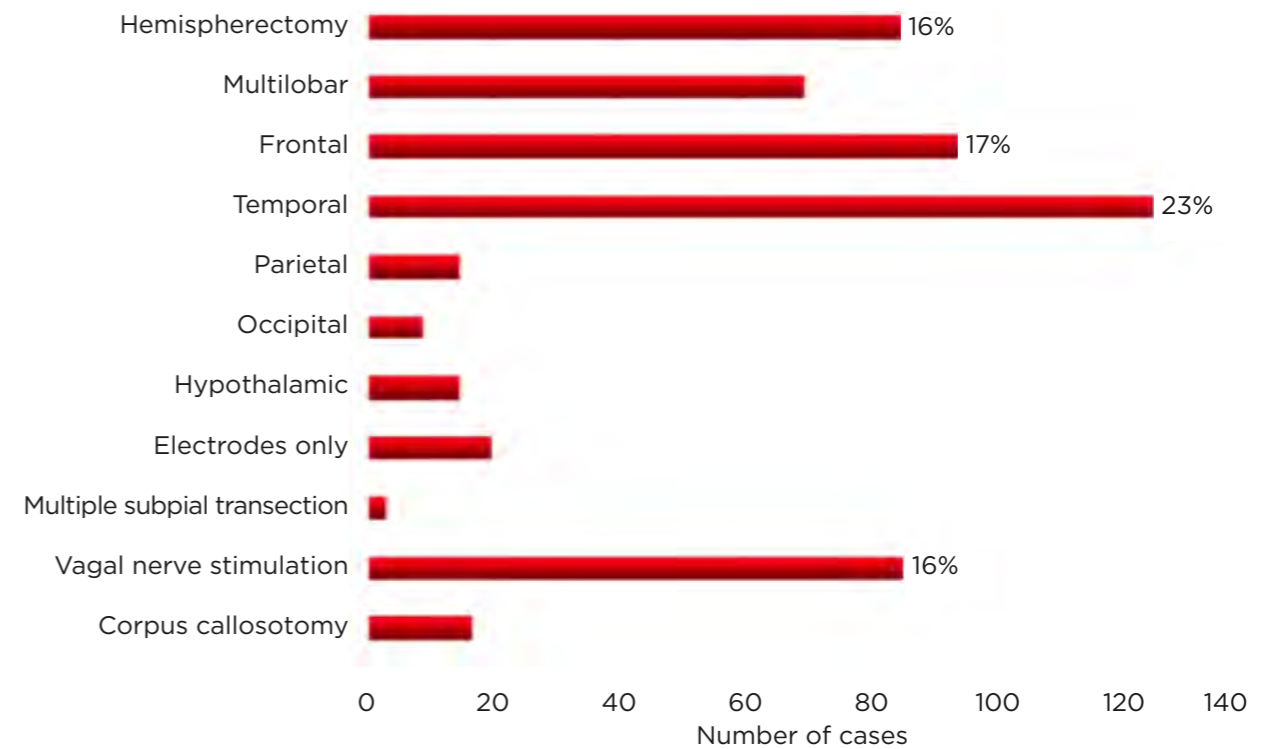


Figure 1B

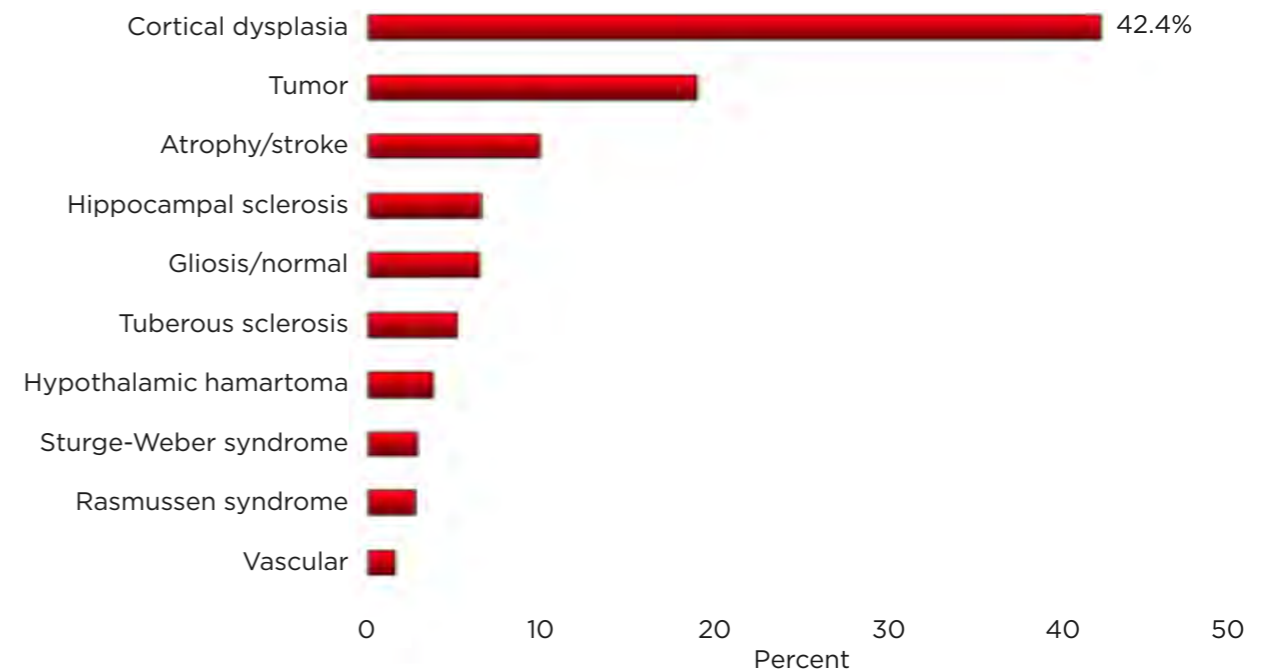


Figure 1. Relative proportions of procedures (A) and pathology (B) in the 2004 ILAE survey of surgical operations in children for epilepsy.

The presurgical evaluation

In all types of resective epilepsy surgery the presurgical evaluation aims to establish the area from which seizures arise and to determine that removal of that area will not further compromise the child i.e. the seizure focus to be resected does not lie in functionally critical cortex. In all children this must start with full clinical evaluation, not only to detail full seizure and AED history but also to determine the degree of any clinical neurological abnormality, and whether the expectations of the family are realistic. The presurgical evaluation may be divided into stage 1, a predominantly noninvasive evaluation, following which some may come to surgery, and stage 2 involving more complex investigation, possibly invasive EEG monitoring. The relative role of technologies available was recently reviewed by the ILAE and a flow chart for evaluation proposed⁹. It is important to emphasise that no investigation provides all the information that is required, and a multidisciplinary approach is mandatory. The extent of investigations required in each individual case will depend in part on the underlying cause, and certainty on concordance.

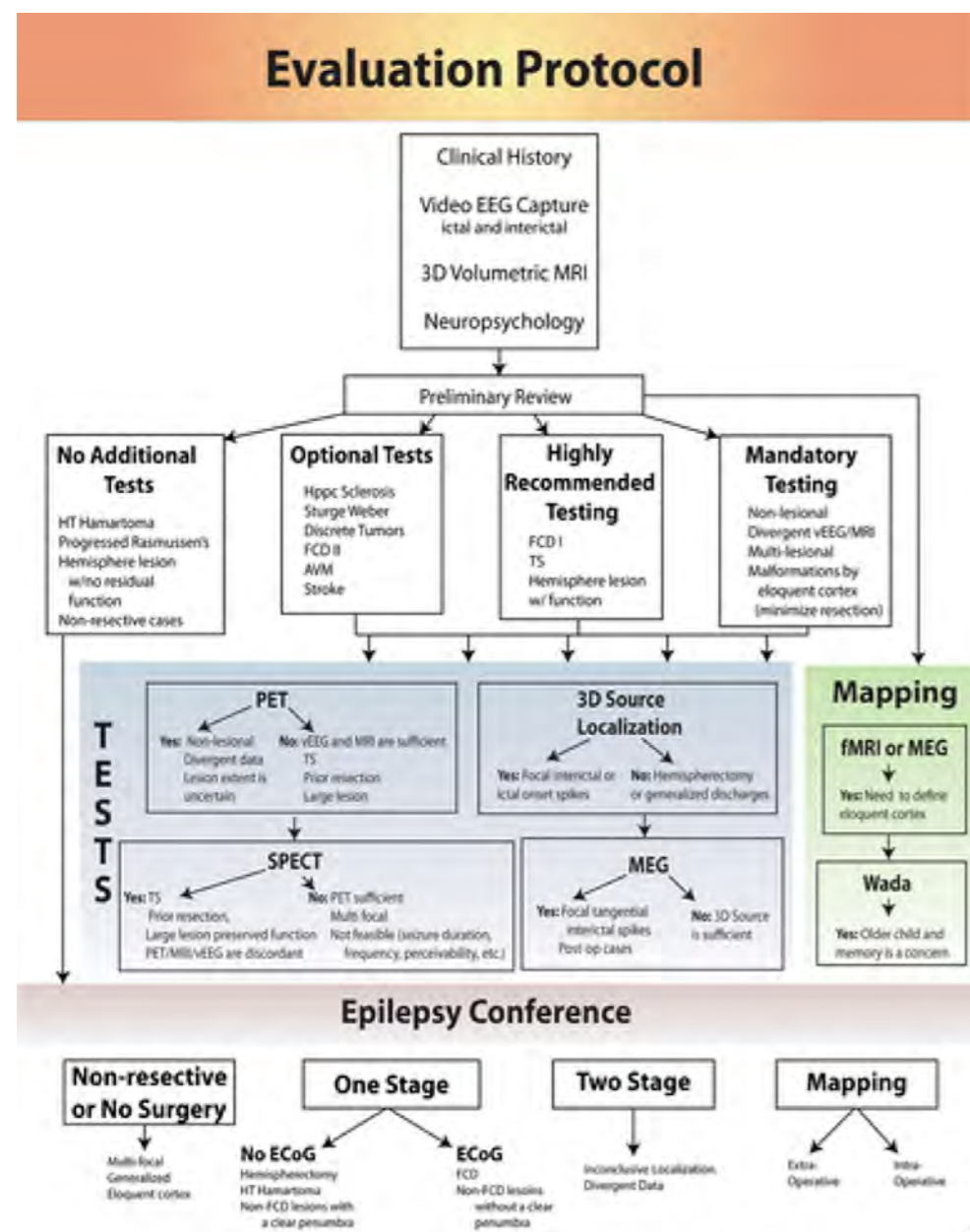


Figure 2: Evaluation protocol as proposed by the ILAE Task Force for Epilepsy Surgery⁹.

Etiology	II EEG					Video EEG					MRI					3D EEG/MEG					FDG-PET					SPECT					ECoG					IEM				
	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U	M	H	O	L	U
Single Lesion																																								
Dev. Tumors																																								
FCD I																																								
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Hipp. Sclerosis																																								
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Post infectious																																								
MRI negative																																								

M, mandatory; H, highly recommended; O optional; L, little use; U, unwarranted.

100%
>85%
60-85%
40-60%
15-40%
<15%
0

The color scale represents the proportion of votes for categorizing each test in each clinical cohort.

Figure 3: Relative contribution of techniques in presurgical evaluation according to pathology⁹.

Focal resection

Optimised MRI (with extensions of this in temporal lobe epilepsy such as T2 relaxometry of the hippocampi, volumetrics), including a 3D data set to determine any evidence of focal brain abnormality. In children aged three months to two years, however, areas of neocortical abnormality may not be apparent in view of incomplete myelination. It is therefore important to consider review of early imaging, as well as repeat imaging with a suitable time interval. However, such abnormalities may be related to functional abnormality with ictal and inter-ictal EEG, as well as ictal and inter-ictal SPECT or inter-ictal PET in selected cases. Magnetoencephalography may also be useful in image-negative older children. In addition, language and/or motor fMRI may be useful in older children where the seizure focus lies close to eloquent cortex.

Hemispherectomy

MRI to assess the extent and pathology of the structural abnormality of the abnormal hemisphere, as well as review of the 'normal' side to make sure there is no evidence of more widespread disease. EEG, ictal and inter-ictal, for lateralisation. Bilateral inter-ictal EEG abnormalities do not preclude consideration for surgery^{10,11}.

Functional procedures

Corpus callosotomy. Clinical history is the main assessment tool, not only to determine seizure type and frequency but to determine social goals. MRI and EEG to determine no evidence of focal disease.

The role of neuropsychology

Since early pathologies often result in reorganisation of function, the major goal of neuropsychological evaluation is to determine lateralisation and focal representation of function. As in adults, cognitive evaluation predominantly involves assessment of core functions such as intelligence, memory, language, reading and writing. The sodium amylobarbitone (amytal) or WADA procedure has a useful role in determining abnormal language representation in adults who may have suffered congenital or early insult to the left hemisphere. It can also be used to assess memory function prior to surgery, to reduce the risk of an amnesic syndrome. However, developments in functional MRI, assessed in combination with full neuropsychology assessment in experienced hands, mean that the WADA test is now rarely performed for assessment of language in children, particularly in the evaluation for temporal resection.

The role of invasive monitoring

Despite the improved techniques in non-invasive presurgical evaluation, there remains a small proportion of children who benefit from invasive EEG monitoring, whether with subdural grids with or without depth electrodes or in stereo EEG. These are children in whom there is concern that the seizure focus lies within a functionally eloquent area, in children with extratemporal epilepsy in whom all data are concordant but there is no structural abnormality on MRI, and those in whom data are suggestive of a single focus but there may be some doubt.

The role of neuropsychiatry

The exact aims of surgery require discussion to review whether expectations on the part of the patient and family are realistic. This has particular relevance in childhood, as the group under consideration is clinically heterogeneous, and outcome aims are diverse.

Table 1. Seizure-free outcome according to procedure and pathology.

	Mathern et al 1999¹⁴ F/up 6m-10 years	Lamberink et al 2015¹⁸ F/up >2 yrs	*GOSH^{15-17,6} F/up >2 year
Hemispherectomy	40/62 (64%)	81%	16/28 (57%)
- Cortical dysplasia	18/26 (69%)		5/15 (33%) ⁸ (HME 20%, other 50%)
- Other	22/36 (61%)		11/13 (82%)
Temporal resection	13/20 (65%)	79.6%	34/59 (58%)
- Hippocampal sclerosis	7/8 (87%)	81.8%	36/42 (86%)
- Cortical dysplasia	6/12 (50%)		18/26 (69%)
- Tumour	6/12 (50%)		18/26 (69%)
Extratemporal/ multilobar resection		70%	
- Cortical dysplasia	16/29 (55%)		22/37 (59.5%)
- Tumour	0		15/22 (68.2%)
- Other	5/13 (38%)		

*GOSH: Great Ormond Street Hospital

In particular, in a young child with severe developmental delay and extremely frequent seizures, the aims of surgery may be more related to improved developmental progress and quality of life with, of course, a reduction of seizures. An older child in normal school is more likely to be seeking seizure freedom and a greater independence. Other associated issues must also be addressed, such as behaviour and any realistic appreciation of change that is unlikely to be predictable. A contract between the professionals and family is desirable prior to the surgical decision.

Outcome

Outcome from epilepsy surgery should be measured not only in terms of seizure freedom, but also in terms of development, neuropsychology, behaviour and quality of life⁷. Seizure freedom is quoted most often in outcome studies no doubt as it is the easiest to determine. Large post-surgical series have shown seizure freedom in 40–87%¹²⁻¹⁴ (Table 1) related more to the underlying pathology than age at onset of seizures, age at surgery, duration of epilepsy or procedure performed, with better outcome seen with acquired as opposed to developmental pathology. Medication reduction is often an aim of parents, and cannot be guaranteed. Around 50% are successfully weaned from AEDs; a recent European collaborative study demonstrated an early wean did not provoke a recurrence that was not inevitable¹⁹. Cognitive benefits were also more likely with a wean of medication²⁰.

With focal resection, the degree of epileptogenic tissue removed is a major determinant of seizure outcome, although the degree to which this can be achieved is also related to the underlying pathology. There is some evidence that the outcome following surgery for developmental lesions may deteriorate with time, that is the likelihood of seizure freedom is less in the longer as opposed to the short term, but that outcome with such lesions may be better with earlier surgery¹⁴. The lesser likelihood of seizure control, however, does not preclude consideration, providing the aims of surgery are realistic and clearly identified preoperatively. Many children are also likely to achieve a substantial reduction in seizure frequency¹³⁻¹⁵ with a reduction in anticonvulsant requirement.

Developmental outcome has been reported as improved following surgery in many studies but has been difficult to quantify, particularly in the very young, as outlined above. As a consequence it is important to obtain as much information as possible about the nature of the epilepsy and the procedure planned, with clear outcome aims clarified with the family.

It is for this reason that a system of categorisation of epilepsy surgery on the basis of the probability of success has been proposed¹¹. This would divide between those in which techniques and prognosis are well established (e.g. conventional temporal lobectomy and hemispherectomy for acquired lesions), those in which prognosis is not so clear-cut (e.g. extratemporal resections, hemispherectomy for developmental lesions, certain temporal lobectomies), and procedures performed on highly problematic individuals in whom surgical intervention may help (e.g. callosal section, subpial transection, trials of partial resection of abnormal tissue).

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CHAPTER 48

Methods of epilepsy surgery

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Pre-surgical evaluation

In order for any epilepsy surgery programme to be effective there has to be a critical mass of staff with the necessary expertise in order to carry out the appropriate evaluations in patients in the pre-operative period, and the post-operative follow up. In both adults and children, following pre-operative evaluation it is essential that the information acquired is critically appraised in a multidisciplinary meeting, not only to determine the suitability of the patient for surgical intervention, but also to attempt to assess the potential risks and benefits of surgery. The meeting should be structured to ensure that the information obtained is carefully assessed and any shortfall in the information identified.

A principal aim of pre-surgical evaluation is to determine the epileptogenic zone and the relationship of this zone to eloquent areas of the brain. The epileptogenic zone is the area of the brain which gives rise to seizures, and the removal of which results in the patient becoming seizure free. No single pre-operative investigation can determine the epileptogenic zone with complete reliability and even when various investigative modalities are combined there may be a variable degree of congruence. When pre-operative investigations have a high degree of concordance it may be possible to recommend immediate surgery with predictable levels of benefit and risk. However, if pre-operative investigations are discordant surgery may be rejected in favour of gathering further information using invasive studies.

Intracranial EEG recording

The aim of invasive EEG recording is to acquire neurophysiological data to support or disprove a hypothesis regarding the site of onset of seizures. The type of intracranial recording depends on the suspected pathophysiological substrate of the epilepsy and its location. Invasive electrodes may be placed either within the brain parenchyma, in the subdural space, or in the extradural space. Electrodes may be used both for recording and for stimulation, allowing assessment of the relationship between the epileptogenic lesion and eloquent cortex.

The first brain electrode implantation took place in the early 1940s, followed in 1946 by the introduction by Spiegel and Wycis of the first stereotactic instrument for human use. Placement of electrodes was initially determined by pneumoencephalography. Angiography was also used in order to avoid major vascular structures when planning electrode trajectories. The additional use of contrast ventriculography allowed the positioning of multiple-depth electrodes in both hemispheres when a wide area needed to be sampled and this approach is still favoured in some centres.

Contemporary frame-based stereotaxy uses either CT or MRI to determine intracranial targets. For depth electrode implantation MRI offers the advantages of high anatomical resolution and allows

selection of trajectories that avoid crossing pial boundaries, thus reducing the risk of intracerebral haemorrhage. Depth electrodes may be placed either orthogonally or radially, the electrodes having between six and ten contact points at 1 cm intervals, to allow recording along the length of the electrode from both deep and superficial points.

In addition to using frame-based stereotaxy, depth electrodes may also be placed using image guidance systems. These have the advantage that the scan may be acquired pre-operatively, either with or without fiducials, at a time more convenient to the patient and the radiology department. It also obviates the need for the application of the stereotactic frame and therefore both simplifies the operation and reduces operating time. The insertion of the electrodes may then be either freehand following the trajectory delineated by the image guidance system, or alternatively they may be introduced using an electrode carrier stabilised to the Mayfield head holder.

In contrast to depth electrodes, subdural strips and grids do not breach the pial boundaries and potentially pose less risk of haemorrhage or cortical damage. Subdural strips can be placed through simple burr holes and used to localise and lateralise both temporal and extra-temporal epilepsy. Subdural grids can record from a larger area of contiguous cortex and are frequently used when epileptogenic lesions are adjacent to eloquent cortex. A wider area of cortex is covered by both strips and grids than by depth electrodes, however if the epileptogenic lesion is situated deep in the cerebral cortex the grid recordings need to be interpreted with care. Similarly, the disadvantage of using depth electrodes is that the area of the brain sampled is usually small and unless seizure onset is seen in a specific electrode or group of electrodes little conclusion can be made regarding the epileptogenic zone. This demonstrates the importance of having a clear plan and objective prior to implantation.

Implantation of a subdural grid over eloquent cortex allows an estimation to be made of the anatomical relationship between the epileptogenic zone and the functional cortex. This allows construction of a homunculus of motor and sensory cortex as well as the mapping of receptive and expressive speech areas. The paradigm for cortical stimulation needs to be adjusted in infants because the thresholds required differ when myelination is immature. As well as direct cortical stimulation, somatosensory evoked potentials can also be used to determine the central sulcus.

The duration of invasive monitoring depends very much on the seizure frequency, the success of any planned stimulation, and patient compliance. In current clinical practice depth electrode implantation is used mainly to determine laterality in seizures of temporal lobe origin and in MRI negative frontal lobe cases, whereas subdural grids are most commonly used for MRI-positive extra-temporal epilepsy and in cases where the presumed seizure onset zone is close to eloquent function. Several weeks of depth electrode recording may be necessary to build a true picture of the patient's seizures and to establish the number of seizures. In contrast, subdural grid recordings seldom extend beyond 10-14 days as the seizure frequency is often higher in these patients, as are the inherent risks of infection.

Invasive monitoring may be terminated at any stage if a clinically significant adverse event is recorded. The risks from monitoring procedures are intracranial haematoma formation as a result of the primary procedure and infection as a consequence of the wires passing through the scalp. These risks can be reduced by careful intra-operative technique and appropriate post-operative nursing care. The use of antibiotics during invasive recording is controversial.

At the end of the invasive monitoring period the data collected are evaluated and the suitability for surgery reassessed. Regrettably a certain percentage of patients will undergo invasive recording but not be deemed suitable for resective surgery, either because the epileptogenic zone could not be satisfactorily determined, because multiple sites were found, or alternatively because the

epileptogenic zone was situated in eloquent cortex. If neither a resective nor a functional procedure is thought possible then the electrodes are removed and the epilepsy is then managed medically.

Invasive intracranial EEG studies are time consuming, expensive, have an inherent complication risk and require numerous personnel. Despite this, the number of patients undergoing these procedures is increasing in recent years. This is being driven by newer imaging modalities such as PET (positron emission tomography), SPECT (single-photon emission computed tomography), MEG (magnetoencephalography) and EEG-fMRI, suggesting possible focal targets for patients with epilepsy. At this time the sensitivity and specificity of these investigations is still to be ascertained and intracranial EEG is needed to prove or disprove the suggested seizure onset zone.

Surgical resection

Epilepsy surgery may be divided into two major categories: resective and functional. The aim of resective surgery is to remove the epileptogenic zone and render the patient seizure free. Based on the discussions at the presurgical meeting, a risk:benefit analysis for each individual patient is determined and the exact nature of the surgical procedure is explained and discussed with the patient in detail. Patients and their families or carers are given both verbal and written information, as well as counselling, so that they are fully informed before written consent is obtained. Once consent is given the surgeon can embark on surgery with a clear clinical objective and surgical strategy.

The surgical techniques employed in epilepsy surgery are relevant to all branches of neurosurgery, with newly-developed technology being particularly useful in this type of surgical intervention. In addition to the basic principles of resection to preserve pial boundaries first described by Sir Victor Horsley a century ago it is also essential to respect the anatomical planes in both the deep and superficial cortex. Stereotaxy or image guidance assists with localisation while accurate tissue removal is facilitated by high quality operating microscopes and the use of the ultrasonic aspirator. At low power the aspirator allows removal of gliotic, tumour and dysplastic tissues while at the same time preserving the pia. The newly available use of interventional MRI allows documentation of lesion resection prior to the termination of any surgical procedure and also allows the surgical navigation software to be recalibrated during the operation, making the procedure more accurate.

Lesionectomy

The increased anatomical resolution afforded by MRI means that many more cortically-based lesions, which give rise to epilepsy, are identified. Small lesions such as cavernomas, focal areas of cortical dysplasia, and indolent tumours such as dysembryoplastic neuroepithelial tumours are recognised as highly epileptogenic and resection of these lesions, particularly when they are extra-temporal, is associated with a high rate of freedom from seizures. As with all resective surgery, success depends on the complete resection of the epileptogenic zone. What may not be clear purely from imaging is the extent to which the tissues surrounding an area of structural abnormality may be contributing to the epileptogenic zone. The extent of perilesional resection is determined by visual inspection and intra-operative electrocorticography and may be further facilitated by the use of image guidance or intra-operative imaging.

Outcome studies have shown that, when the cortical lesion lies within the temporal lobe, resection of the lesion alone results in a significantly poorer outcome than in extra-temporal cases. It is probable that this inferior outcome is a result of the proximity of the cortical lesions to the mesial temporal structures and associated dual pathology, i.e. the presence of hippocampal sclerosis alongside the structural lesion. When lesions occur in the temporal lobe a careful preoperative assessment of hippocampal size and signal, as well as the patient's neuropsychological function, should be carried out. Careful consideration has to be given to the potential benefits and risks of lesionectomy and the removal of the mesial temporal structures, particularly when the lesion lies

within the dominant temporal lobe. It may be worth considering a staged approach to resection, whereby a lesionectomy is performed initially in the knowledge that, should this fail, a subsequent wider procedure may be performed.

Temporal lobe resection

Penfield was the first to recognise that, in patients with seizures of temporal lobe origin, the temporal lobe together with the hippocampus and amygdala could be removed safely and effectively. This procedure now accounts for approximately 50% of operative procedures carried out in specialist epilepsy centres. This is primarily due to the stereotypical semiology of seizures arising from the temporal lobe, and in particular the mesial temporal structures. It is also due to the ease with which the diagnosis can be made electrographically and the tremendous contribution made by MRI in the pre-operative diagnosis of hippocampal sclerosis.

In the 1950s, Falconer at the Maudsley Hospital described anatomical temporal lobe resection. This standardised procedure involved the removal of a large amount of temporal neocortex 'en bloc' with the mesial temporal structures. The resection of a large amount of temporal neocortex has the disadvantage of producing significant neuropsychological deficits as well as a superior quadrantanopia. For this reason there has been a tendency to reduce the size of the neocortical resection, either according to the method described by Spencer or by carrying out one of the variously described forms of selective amygdalohippocampectomy. Selective amygdalohippocampectomy may be performed anatomically or by using intra-operative image guidance. When the causative pathology is hippocampal sclerosis it is likely that the extent of mediobasal resection, rather than the neocortical resection, is the determinate factor in outcome. Despite this there is still controversy about the different approaches adopted although this is probably due more to the surgeon's preference than scientific study. Nonetheless, the familiarity of a specific approach or technique does improve outcome and lower morbidity and this should therefore be a serious consideration when determining surgical strategy.

Despite the dramatic advances in pre-operative diagnosis the outcome from temporal lobectomy has only slowly improved. In the case of hippocampal sclerosis our seizure-free rate at the National Hospital for Neurology and Neurosurgery is approximately 75-80% while for lesions it is approximately 70-75%. In dominant temporal resections deterioration in verbal memory is most common in patients with a preserved memory pre-operatively. Quadrantanopia occurs in approximately 10% of patients and in 5% this is severe enough to render the patient ineligible for a driving licence. Post-operative depression is seen in many patients and although commoner in patients with a previous history of psychiatric problems it may occur de novo.

Extra-temporal resections

This category includes single and multi-lobar resection, either for diffuse pathology or in patients in whom the MRI is negative. In order to determine the extent of a lobar or multi-lobar resection it may be necessary either to carry out chronic invasive recording or alternatively to use a combination of electrocorticography and evoked potentials intra-operatively. Depending on the pathology, large resections may be necessary to effectively remove the epileptogenic zone and, under these circumstances, care must be taken not to impinge on eloquent cortex, unless the pre-operative discussions have determined that neurological deficit is preferable to persistent seizures.

The outcome and morbidity in these cases is determined by the pathology and anatomical position of the epileptogenic zone. The extent of the resection may also influence the neuropsychological sequelae of a resection, but in many cases is predictable.

Hemispherectomy

Hemispherectomy was first described in the management of malignant cerebral tumours. This established the surgical technique but quickly demonstrated that the indications were inappropriate. In 1938 McKenzie described the application of the procedure in a patient with medically intractable seizures and behavioural problems. Over the next 25 years the procedure was widely used in patients with intractable seizures. The inevitable consequence of a hemispherectomy is a profound neurological deficit, including hemiplegia and hemianopia, however many of the patients considered for surgery already have these neurological deficits. In the 1960s the original anatomical procedure fell into disrepute as the procedure caused long-term complications in many patients such as hydrocephalus, and in some cases resulted in death.

As a result alternative techniques for either obliteration of the surgical cavity or disconnection of the hemisphere were developed. First, Rasmussen described a functional hemispherectomy in which the temporal lobe and central cortex were removed and the corpus callosum and frontal and occipital cortex disconnected. This procedure was subsequently made less invasive by Delalande and Villemure who described different techniques of hemispherectomy. The consensus view of these alternative techniques is that, when properly performed, the outcomes are very similar if disconnection and not resection is performed.

The success of hemispherectomy depends on the underlying pathology, with excellent outcomes expected for pathologies such as Rasmussen's encephalitis and focal infarcts, and a poorer outcome expected in patients with hemi-megalencephaly.

Functional procedures

The objective in functional epilepsy surgery is to palliate rather than to cure the epilepsy. Functional procedures should only be considered once resective surgery has been deemed inappropriate, or to carry too great a risk.

Corpus callosotomy

Corpus callosotomy was first developed in the 1940s following the observation that in patients undergoing transcallosal exploration of tumours, seizures were reduced in frequency. The primary indication for corpus callosotomy is atonic drop attacks, although it has been used to good effect in other epilepsy types and syndromes. The major concern with corpus callosotomy is the risk of either immediate or delayed symptoms of disconnection. In order to prevent or minimise the risk of a disconnection syndrome the callosotomy should be carried out in two stages, with the anterior two-thirds of the corpus callosum being divided at the first operation and the posterior third divided if and when the callosal section is completed. In children under the age of 12 years there is no evidence to suggest that long-term disconnection syndrome occurs and for this reason a one-stage complete callosotomy is carried out whenever possible in this younger age group.

Careful surgical technique is essential for this procedure and great attention needs to be paid to preservation of the vascular anatomy, particularly the bridging veins, and retraction should, as always, be kept to the minimum.

Stimulation

Since the introduction of deep brain stimulation there has been a continuing quest to determine its efficacy in the management of epilepsy. The numbers of patients who have undergone deep brain and cerebellar stimulation for epilepsy are small and results to date have not been dramatic. However, with the continuing advancements in stimulator technology and the improved accuracy of implanting electrodes, this may be a continuing source of development in the future. A recently

reported randomised trial of the anterior nucleus of the thalamus has shown efficacy comparable with vagal nerve stimulation (VNS).

Peripheral stimulation in the form of VNS has attracted considerable interest since it received FDA approval in the United States in 1997 and is used as a palliative procedure in patients for whom resective surgery is not suitable. Although not wholly elucidated, the pathophysiological basis of periodic vagal nerve stimulation seems to be stimulation of autonomic nervous pathways. Besides intermittent stimulation, on demand stimulation can be achieved by the patient or companion.

At surgery the left vagal nerve is used in order to avoid cardiac side effects, and the electrode is placed on the nerve in the neck between the common carotid artery and the internal jugular vein. Side effects include hoarseness and coughing during stimulation and discomfort in the neck. The median reduction of seizures from vagal nerve stimulation is 45% at one year. While relatively few patients become seizure free with VNS, there are suggestions that efficacy and quality of life further improve over time. An extensive patient registry and ongoing clinical evaluation to provide a growing database of information will ultimately allow a cost:benefit analysis of this therapy.

Multiple subpial transection

This technique was first described following animal research by Morel in which he demonstrated that superficial incisions in the cortex could reduce seizure propagation while preserving function. This followed recognition that the anatomical organisation of the cortex was vertically oriented, while spike propagation occurred horizontally. In addition, intragrisular incisions in the cortex had been shown to preserve the vascular supply, thus preserving function. A critical volume of cortex was also shown to be necessary for spike generation.

Multiple subpial transection is a technique advocated for the palliation of seizure generation and propagation within eloquent cortex, with the objective of maintaining anatomical function while reducing epileptogenesis. It is frequently used in conjunction with wider resections which makes an accurate assessment of outcome following multiple subpial transection difficult. There are a few specific indications including Landau-Kleffner syndrome in children in whom, following demonstration of a predominant epileptogenic focus following a methohexital suppression test, multiple subpial transection may result in improvement in both language, communication and behaviour.

Exploratory and future techniques

Gamma knife surgery

Following on from the 'proof of concept' that selective procedures on the medial temporal lobe could be effective in the surgical management of epilepsy, Regis has pioneered the concept of creating a stereotactic radiosurgical lesion to the amygdala and hippocampus instead of performing a resection. Increase in efficacy comparing doses of 20 and 24 Gy has been demonstrated, with a two-year seizure-free outcome similar to resection reported in a carefully selected cohort. The theoretical benefits are that the patient avoids an open surgical procedure and that the psychological/psychiatric consequences may be less. These must be balanced against the risk of post-procedure swelling, delay to seizure freedom, increase in simple seizures one year following treatment, and reported increase in visual field deficits and the unknown long-term risk of radiation. The ROSE study, a randomised multicentre trial, is presently taking place comparing surgery and gamma knife in medial temporal lobe epilepsy. Other forms of anatomical lesioning, such as with a laser, are presently being investigated. The advantage of these techniques is their immediate effect.

Neuropace RNS™

The RNS neurostimulator is a programmable, battery powered, microprocessor-controlled device that delivers a short train of electrical pulses to the brain through implanted leads. The stimulator is designed to detect abnormal electrical activity in the brain and respond by delivering electrical stimulation to normalise brain activity before the patient experiences seizure symptoms. The neurostimulator is implanted in the cranium and connected to one or two leads that are implanted near the patient's seizure focus. The device monitors the patient's electrical activity by connection to an implanted strip electrode on the brain surface. In theory the device can be taught to recognise the onset of a patient's seizure.

Paediatric epilepsy surgery

The role and importance of the multidisciplinary meeting in determining surgical suitability and surgical strategy has already been stressed. In the case of children this means that neurophysiologists, neuropsychologists, neuropsychiatrists, and neurologists must have specific experience in managing children with intractable epilepsy. A dedicated paediatric service is also vital in the peri and post-operative periods. Surgery should be carried out in a paediatric centre and, to ensure the safety and well-being of the patient, the services of a paediatric neuro-anaesthetist are paramount. There are very specific anaesthetic requirements, particularly when electrocorticography is required, and the anaesthetic technique employed should be carefully selected.

Furthermore, when dealing with cortical dysplasia, blood supply to the dysplastic area may be extremely abnormal with intra-operative blood loss becoming a critical issue. This is the case particularly in patients with hemimegalencephaly, in whom the dysplastic hemisphere may have a grossly disorganised blood supply and venous blood loss during the procedure can pose a very significant hazard.

Many patients with severe, refractory epilepsy suffer from delayed neurological development and also impaired psychosocial adaptation and behaviour. For this reason many patients undergoing epilepsy surgery remain in the care of the paediatric epilepsy services despite being above the age of sixteen. The skills of the paediatric team are therefore also of benefit to young adults. Sympathetic management from a medical and nursing standpoint is essential to ensure that the experience of the hospital admission and surgical intervention is as smooth and as atraumatic as possible.

Surgical follow-up

There are many facets of outcome from epilepsy surgery; seizure control, neuropsychological development, neurological deficits, quality of life and psychosocial adjustment. It is regrettable that many publications address the outcome following surgery after only a very short time. Long-term studies of all patients are required, with a follow-up of at least two years. It is also important to realise that seizure status may not necessarily indicate a good outcome, and quality of life measurements are increasingly used to determine the efficacy of surgical intervention. Some patients with long-standing epilepsy will have few improvements in their quality of life. Over time epilepsy affects a patient's pattern of behaviour and also their social interaction; and these effects may be irreversible. This would suggest that earlier surgical intervention may be beneficial. Since we are increasingly able to detect epileptogenic lesions in children and predict patterns of clinical progress, this will without doubt lead to increasing emphasis on surgery in childhood.

Suggested reading and reference books

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CHAPTER 49

Vagus nerve stimulation

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Overview

Vagal nerve stimulation (VNS) was originally delivered to patients over 30 years ago with the first patient being implanted in 1988. European Community approval was granted in 1994 and USA (FDA) commercial approval in 1997¹. Since then tens of thousands of devices have been implanted and by 2015 more than 100,000 patient years of experience had been accumulated². VNS currently has a licence in Europe and the UK for the adjunctive treatment of epilepsy refractory to antiepileptic medication. The UK NICE Guidelines for Epilepsy (2012) suggest VNS is indicated 'for use as an adjunctive therapy in reducing the frequency of seizures in adults (and children) who are refractory to antiepileptic medication but who are not suitable for resective surgery'. NICE specifies that VNS is indicated for patients in whom focal or generalised seizures predominate. The US licence in epilepsy is for refractory focal epilepsy in patients over the age of 12.

VNS is implanted to reduce the frequency and severity of seizures. That the VNS magnet can be used to administer an extra stimulation at the onset of the seizure can be additionally beneficial in some patients. Since its initial implantations for epilepsy, VNS has been trialled in a variety of other medical conditions. In particular, the observation that co-existing depression in epilepsy patients seemed to improve with VNS led to VNS now also being licensed for treatment-resistant depression in adults and the American Academy of Neurology have recommended that VNS may be considered for improving mood in adults with epilepsy³. Other potential therapeutic roles in anxiety, dementia, tremor, heart failure, obesity, stroke and even rheumatoid arthritis are being explored.

Mechanism of action

Theories as to how VNS mediates its effect include direct activation, neurotransmitter and neuropeptide modulation influencing ictal discharge, pre-ictal changes and arousal^{4,5}. VNS can alter cytokines and a recent study also demonstrated that VNS stimulation in children increased levels of anthranilic acid, a neuroprotective and anticonvulsant metabolite⁶.

As many as 80% of vagus fibres are afferent and the parameters used in clinical practice preferentially stimulate these smaller fibres over the efferents. Afferent pulses reach the nucleus tractus solitarius (NTS), synapsing bilaterally. The NTS projects to the thalamus, hypothalamus, locus coeruleus, reticular activating system, midline raphe, limbic system and secondarily to the cortex. In a kindling model of epilepsy, VNS was shown to prevent lowering of seizure threshold compared to control animals⁷. In rodents treated with kainic acid VNS promoted neurogenesis in the dentate gyrus of the hippocampus while in a maximal electroshock rat epilepsy model, VNS therapy was no longer effective as an anticonvulsant when noradrenergic pathways were depleted by lesioning of the locus coeruleus. A cat amygdala kindling seizure model has also suggested

a partial anti-epileptogenic effect of VNS. Positron emission tomography (PET) scanning showed increased blood flow in the thalamus, hypothalamus, and the insular cortex with decreased blood flow in the amygdala, hippocampus, and posterior cingulate. VNS induced forebrain Fos, a nuclear protein expressed under conditions of high neuronal activity. Further, VNS has also been shown to reduce anhedonia in rats treated with kainic acid, lending support to the use of VNS in depression⁸. However, the exact molecular mechanism by which VNS exerts its effect is uncertain⁹.

Some interesting insights into the action of VNS in humans have been explored with EEG recording. A small study compared five patients who had responded well to VNS implantation to five patients in whom VNS had not been beneficial. EEG recordings five years after implantation showed that patients who had benefited had a decrease in gamma band frequency desynchronisation¹⁰. More recently another small study has shown that patients who respond to VNS therapy demonstrate a shift in EEG architecture towards a more efficient configuration¹¹ raising the possibility that chronic VNS offers some stabilisation of neuronal networks. Studies have also begun to explore whether there are EEG signatures, such as levels of cortical synchrony¹² that might better predict response to VNS¹³. Recently, animal studies have shown that VNS can induce hippocampal theta rhythm, which is involved in memory consolidation but if this might be related to antiepileptic effects remains uncertain.

VNS – device and process

Originally only a single manufacturer (Cyberonics) had rights to produce the device but this restriction has now expired, and a number of devices are becoming available. In some experimental animal models stimulating the right vagus nerve produces cardiac dysrhythmias so VNS is only licensed for implantation on the left in humans. The generator is usually implanted in the left upper chest with the electrodes placed around the left cervical vagus. Afferent pain fibres may be activated, especially at higher levels of clinical stimulation, producing discomfort in the throat, but even at normal therapeutic levels patients are usually aware when the device activates due to a sensation in the throat.

An electrical test of the device is performed intra-operatively, but the device is usually activated some time post-operatively, often at the first outpatient follow-up. Continuous electrical stimulation of the vagus nerve in animal models has been shown to produce fibrosis and ultimately failure of the nerve, so stimulation is provided in an intermittent manner. Typically, the VNS device is initially set to provide 30 seconds' stimulation every five minutes. The device is programmed externally (output current, signal frequency, pulse width, signal on- and off-times) and adjustments are made on the basis of tolerability of side effects and clinical efficacy.

In addition to the continuing cycling on and off, it is possible to manually activate the device by passing a magnet over the generator box. Patients or carers can use this when a seizure starts, and in some the magnet seems to shorten or limit the extent of the attack. Commonly the current delivered following magnet-induced activation is set slightly higher than the baseline level. A review of whether magnet activation was actually beneficial was provided by Fisher and colleagues in 2015¹⁴. Through examination of 20 studies involving 859 patients, benefit from the magnet was reported in a weighted average of 45% (range 0–89%) and seizure cessation in 28% (range 15–67%). One study did report a worsening of seizures with magnet activation in an isolated case. As the authors highlighted, voluntary activation of the magnet has several limitations, including patients not being able to activate the magnet if they are asleep, immobile or the magnet is not immediately accessible.

The magnet also provides a means for the patient to deactivate the device. If the magnet is placed over the generator box and it remains there for more than a few seconds the VNS switches off.

When the magnet is subsequently removed, it reactivates at the previous settings. This may be used by patients to investigate whether a symptom such as cough is related to the device or to some unrelated cause. Similarly, the device can be switched off for certain occasions when patients may wish, for example, to make a speech and are keen to avoid any fluctuation in voice quality.

Regular follow-up is needed, with gradual current adjustment to achieve maximum benefit in a similar way to adjustments of antiepileptic drug (AED) dose. Battery life depends on output and magnet use. The device should be checked regularly and an early replacement indicator (ERI) or 'near end of service' (NEOS) alert will warn the clinician of impending battery exhaustion after which the pulse generator will need to be replaced. A rechargeable battery is in development but is not yet in mainstream use.

Precautions and adverse effects

As with all surgical procedures, patients must be fully informed of the potential risks and the long-term consequences of VNS insertion. Despite little vagal visceromotor activity during therapeutic VNS in humans, caution is advised in patients with heart disease and severe asthma. One study concluded that 'long-term vagus stimulation in patients without concomitant lung disease does not induce any significant changes in FEV1. However, in patients with obstructive lung disease, intense vagus stimulation can cause a deterioration of lung function'¹⁵. It is recommended that there is minimal handling of the vagus intra-operatively. Transient bradycardia or sinus arrest may occur during the lead test in 0.1% of cases but is not necessarily a contraindication to switching on the device after an interval. Infection of the lead or generator site, likely the most serious adverse effect, may occur in up to 3% requiring removal of the device in about 1%. Lead breakage may occur. Horner's syndrome, unilateral facial weakness and vocal cord paresis have been reported. Stimulation and, to a lesser extent, implantation may be associated with hoarseness, cough, dyspnoea, pharyngitis, paraesthesia and pain. The main side effect noted by patients is the hoarseness and change of voice during the stimulation phase. Pre-existing dysphagia may be exacerbated. Recent studies report worsening of or new onset sleep related breathing disorders such as obstructive sleep apnoea (OSA)¹⁶ following implantation of VNS. It is advisable to include objective and subjective sleep parameters in the initial evaluation and follow-up of patients considered for VNS due to the risk of sleep apnoea as OSA may exacerbate seizures.

If a patient requires removal of the device for infection or if removal is requested due to lack of efficacy, it is usual to remove the generator box only and to leave the lead in place. The lead can be removed but this entails more difficult surgery and carries some risk of a hoarse voice owing to injury to the vagus nerve.

The common side effects of ataxia, dizziness, fatigue, nausea and somnolence that are seen with AEDs were absent from the list of statistically significant side effects of VNS in a Cochrane review¹⁷.

Outcome data was recently reported from 26 pregnancies in women treated with VNS¹⁸. Although obstetric interventions (such as c-sections) were more common, there were no clear indications to suggest VNS-related teratogenicity but in view of the small number, the authors felt that there was not enough data to draw any firm conclusions.

Practical considerations

Strong electric or magnetic fields may damage the generator and should be avoided. A detailed account regarding risks associated with defibrillation, lithotripsy, therapeutic ultrasound and therapeutic and surgical diathermy can be found on the website <https://www.livanova.cyberonics.com>. The system is not affected by home microwave ovens or mobile phones. Airport security

systems and shop theft detectors may be activated by VNS although there are no reports of the VNS itself being affected.

There is some concern regarding limitations of new generation MRI in those with VNS implantation, including those where the battery pack has been removed but the wire remains. The potential risks of performing MRI on patients with an implanted VNS include heating effects, especially of the stimulation electrodes, inadvertent resetting of the device or magnet mode activation, image distortion and artefacts, magnetic field interactions and device malfunction or damage. If performing an MRI scan, VNS output should be set to zero beforehand and reset afterwards, meaning that an appropriately trained person must be available. VNS is approved in MRI scanning using only transmit-and-receive type head coils at both 1.5 and 3 Tesla field strength. Some modern head coils are of the phased-array type which should not be used.

In practice, good diagnostic quality brain scanning can be achieved if appropriate precautions are in place (for example de Jonge *et al.*, 2014)¹⁹. However, body or extremity imaging (receive-only coils) and experimental brain protocols may not be risk-free, even if the generator has been explanted and only the wire remains. Work is being carried out to develop full MRI compatibility, but restrictions remain at present. It is advisable to consult the device manufacturer if there is any doubt before performing MRI.

Effect in epilepsy

VNS appears to have an abortive and a prophylactic effect, both acutely and chronically in epilepsy. It is effective in various animal seizure models. Although the double-blind studies were in partial epilepsy, it appears to be broad spectrum. It has been implanted in a variety of syndromes, including idiopathic generalised epilepsy and Lennox-Gastaut syndrome²⁰, with broadly similar results²¹.

A Cochrane review (2001) addressed the efficacy of high-level versus low-level stimulation, the latter as active control¹⁷. The review only included the two early short-term randomised and double-blind trials^{22,23}. The review concluded that 'results of the overall efficacy analysis show that VNS stimulation using the high paradigm was significantly better than the low stimulation'. The overall odds ratio (OR) for 50% responders was 1.93 (1.1, 3.3). Any beneficial effect of low stimulation would tend to reduce the high stimulation OR compared to placebo. Although direct comparisons may not be valid, of interest are ORs reported in meta-analysis of studies of some add-on AEDs. For example ORs reported for 50% responders relative to placebo were, in order of increasing magnitude: 1.59 (0.91, 2.97) for remacemide, 2.29 (1.53, 3.43) for gabapentin, 2.32 (1.47, 3.68) for lamotrigine, 2.46 (1.61, 3.79) for zonisamide, 2.51 (1.88, 3.33) for oxcarbazepine, 3.78 (2.62, 5.44) for levetiracetam and 4.22 (2.80, 6.35) for topiramate²⁴⁻²⁷. Thus, VNS in early studies appears to have a short-term effect in refractory patients approaching that of some of the AEDs. It is less effective, however, in the short or long term, than resective surgery in well-selected cases, including temporal lobectomy for mesial temporal sclerosis.

More recently there has been an updated Cochrane review (2015) of the role of VNS in focal epilepsy²⁸. Again, the objective was to determine the efficacy of high-level to low-level stimulation. Four trials were included in the meta-analysis and high-level stimulation was shown to be 1.5 times more effective than low-level stimulation. Overall VNS was well tolerated, with the side effect profile very similar to that previously reported. Hoarseness and dyspnoea were amongst the more common side effects and these were seen more frequently with higher levels of stimulation²⁸. Similar findings have also been reported elsewhere²⁹, although some have been more circumspect as to whether VNS does offer significant patient benefit above best drug therapy³⁰.

Patients are generally aware of stimulation due to a feeling in the throat, so it is not possible to fully blind patients to whether VNS is on or off. Nevertheless, the two double-blind randomised controlled trials in partial epilepsy were carried out when the device was first introduced and presumably the patients may have been less informed as to the expected effects^{22,23}. Later studies involve large numbers of patients but are open label. The mean reductions of seizure frequencies of 24.5% and 28% observed at three months in the randomised trials indicate rather modest benefits.

By contrast with AEDs whose benefits tend to reduce with time, open studies consistently show an increasing effect of VNS with time. For example, at one year a median seizure reduction of 45% has been shown, with 20% of patients achieving a greater than 75% reduction^{1,23,24}. More striking, however, are the longer-term studies with progressive improvement in the seizure frequency for more than ten years. For example, Kuba *et al* found 85 out of 90 patients implanted continued VNS at five years with a median seizure reduction of 56% and with 64% enjoying a 50% or greater reduction³¹. By ten years Elliott *et al* found a 75% reduction in 65 patients¹⁸ and in following 347 children, Orosz and colleagues showed a responder rate (>50% reduction in baseline seizure frequency of principal seizure type) of 32.5% at 6 months, 37.6% at 12 months and 43.8% at 24 months³². In the Orosz study there was also a statistically significant correlation between increased response rate and total charge delivered by the VNS. Nonetheless, periods of seizure freedom greater than one year are only experienced by about 5-10% of patients in the open studies and may be subject to publication bias³³.

An intriguing recent single centre study compared two groups of clinically matched patients 18 months after VNS implantation. In one group patients could have their medication altered at the discretion of their neurologist and in the second group, no AED changes were permitted. The authors found that the group where AEDs were not altered were more likely to achieve greater than 50% reduction in seizures suggesting that changes in medication did not, overall, improve outcomes. Furthermore, they suggested that changes in AEDs could make it more difficult to optimise the VNS settings³⁴.

A mortality study by Annegers³⁵ showed that the excess mortality associated with refractory epilepsy was lower with longer-term follow-up after VNS implantation (standardised mortality ratio, or SMR, of 3.6 with extended follow-up compared to the previous finding of an SMR of 5.3). Moreover, when VNS experience was stratified by duration of use, the rate of sudden unexpected death in epilepsy (SUDEP) was 5.5 per 1000 over the first two years and 1.7 per 1000 thereafter. This finding was not, though, confirmed in a more recent study showing that VNS did not appear to lower the risk of premature death or rate of SUDEP³⁶.

In a cost analysis study³⁷, unplanned direct hospital costs before and after VNS implantation showed an annual reduction of some \$3000 US per study patient, irrespective of whether the patient was classified as a responder (in this study defined as experiencing 25% or greater reduction in seizure frequency). Other studies have reported a significant decrease in epilepsy-related direct medical costs in VNS-treated patients³⁸ and recently a large study has confirmed a progressive and substantial reduction in healthcare costs following implantation, with the surgery and device costs being offset by the savings by 18 months³⁹. More recently in the UK, Camp and colleagues analysed hospital episode statistics (HES) data in the UK and found that, for patients with VNS implantation, while in-patient admissions decreased, there was an increase in out-patient attendance for review and adjustment of VNS stimulation parameters⁴⁰. Nonetheless, the authors concluded that there were lower average medical costs after VNS implantation compared to before. This does, though, contrast with de Kinderen and co-workers suggest that in children with pharmaco-resistant epilepsy, ketogenic diet may be more cost-effective than VNS although neither the diet nor VNS were thought cost-effective when compared to standard medical care⁴¹. These authors did emphasise that VNS and ketogenic diet are likely to continue to have a role in population sub-groups and

further that longer term studies that examined parameters such as quality of life, rather than just seizure frequency, were needed.

Special groups

There are many case series of the use of VNS in particular syndromes, often purporting benefit that is not necessarily replicated in other studies. Notably, a recent review concluded that VNS could not currently be recommended in refractory status epilepticus⁴². Similarly review of published data would suggest that corpus callosotomy is a more effective treatment for pharmacoresistant drop attacks than VNS⁴³. There does, though, appear to be some evidence of specific benefit in Lennox-Gastaut Syndrome^{3,44} and there are repeated reports of improvement in alertness and mood, most noticeable in those with learning difficulty. Patients with learning difficulties, both adults and children, may therefore be especially suitable for VNS insertion⁴⁵.

Future advances

A potentially promising development in VNS technology is the Aspire SR VNS device which was introduced and approved for CE Mark in February 2014. Aspire SR is responsive to heart rate, giving an extra stimulation when detecting ictal tachycardia. The device is somewhat larger than the previous model, therefore requiring a larger skin incision, and intra-operative testing can take longer⁴⁶. However, the possibility of automated additional stimulation at the onset of a seizure would seem worthwhile, particularly for patients who may not be able to activate the stimulator themselves for example due to lack of warning before loss of consciousness or who may not be able to carry out the stimulation.

Another novel development is of transcutaneous VNS. This stimulates the auricular branch of the vagus, which supplies the skin of the concha of the ear and is a non-invasive device. Benefit has been shown to seizure profile in small studies and there are minimal reported complications or side effects⁴⁷⁻⁴⁹. However, larger studies are needed to fully evaluate the effect of transcutaneous VNS. Likewise, there is minimal data currently available to evaluate the effect of trigeminal nerve stimulation on seizures or neuropsychiatric disorders. At the moment, tVNS has not been approved for treatment on the NHS.

Neurostimulatory therapies in epilepsy also now include responsive neurostimulation (RNS) and deep brain stimulation as well as VNS. RNS is not currently available in the UK although is becoming widely utilised in the United States, perhaps particularly in patient who have bilateral hippocampal onset to seizures and are therefore amenable to targeted and responsive stimulation to both hippocampi. Patients with seizure onset zone in or near eloquent cortex that cannot safely be removed may also be particularly suitable for this type of treatment. A current overview of choices of neurostimulation available and an algorithm to help determine choice of therapy is provided by Gooneratne and colleagues⁵⁰. It is also important to acknowledge that VNS is gaining traction in low to middle income countries with, for example, studies reporting longer term data from the Middle East in particular.

Summary

VNS is now established as a safe procedure with clear, clinically useful and sustained benefits, particularly in the medium to long term. It is recommended that VNS is considered in patients with pharmacoresistant epilepsy who are not suitable for resective surgery. VNS may have a particular benefit in patients with learning difficulties and may also offer benefit to mood in patients with epilepsy. Caution however should still be exercised in older populations with potential co-existing

cardiopulmonary disease where experience is still limited. Review of potential sleep related breathing disorder is also recommended as this may exacerbate seizures.

VNS offers different advantages and disadvantages to standard AEDs and its profile may preferentially suit certain patients. Compliance is ensured and VNS does not typically associate with central nervous system side effects. VNS is unlikely to render patients seizure free and continued use of antiepileptic medication is usually necessary. The cost-benefit analyses in severe epilepsy are reasonably compelling and may lead to a more widespread use in patients with frequent hospital admissions or who are on polypharmacy.

The increasing utilisation of responsive VNS and further development of transcutaneous VNS offer exciting possibilities. These advances, coupled with deep brain stimulation in epilepsy, mean that the role of neurostimulation in drug-refractory epilepsy is likely to continue to expand.

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CHAPTER 50

Outcome of surgery

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Any consideration of outcome from surgery should include not only seizure freedom rates but also neuropsychological, neurological and psychiatric impacts.

The successful outcome for epilepsy neurosurgery depends upon:

- type of operation
- site of the lesion
- nature of the lesion
- results of pre-operative assessment (especially the degree of congruence)
- experience of the centre/surgeon carrying out the surgery.

The risks depend upon these factors, but the risks of any additional investigations also need to be incorporated (e.g. the risks of intracarotid amygdala, depth electrodes etc).

Risks of pre-operative investigation

Even apparently non-invasive investigation can carry some risk. Video-EEG telemetry can carry some risk if drug reduction is undertaken in order to record an adequate number of seizures. Drug reduction can produce more severe seizures that can occasionally result in post-ictal psychosis, peri-ictal injury and, rarely, death. Thus consent is necessary for drug reduction in video-EEG telemetry units with the potential risks and benefits carefully explained to the patient.

Invasive investigations carry more obvious risks:

- A standard intracarotid sodium amygdala test results in permanent neurological change in less than 0.5%, but transient neurological deficits can occur in more (up to 3%).
- Subdural electrodes frequently result in mild-to-moderate complications. The risk of infection is approximately 3-5%; over a quarter of patients develop an aseptic meningitis - usually restricting recordings to 10 days or less.
- Intracranial electrodes are mainly complicated by infection and haematoma. The risk is dependent on the number of depth electrodes and their placement. The risk is approximately 1-2% for most studies.

Outcome of operation by type of surgery

Temporal lobe surgery (anterior temporal lobectomy, selective amygdalo-hippocampectomy) results in approximately 70% of patients becoming seizure free at 2 years after operation (this figure may be even higher in those with hippocampal sclerosis and concordant investigations), and 20% are improved. Approximately 50% of patients remain seizure free for 10 years. The overall mortality of temporal lobectomy is less than 0.5%, and the risk of permanent hemiparesis less than 1%. A transient hemiparesis can occur in up to 5%. The impact of the operation on memory depends upon the age of the patient, whether the operation is on the dominant temporal lobe and the preoperative memory function. Visual field defects that prevent driving can occur in over 5% of those undergoing mesial temporal resection. Psychosis and depression are not uncommon sequelae following temporal lobe resection, and patients should be warned of the possibility of these following surgery.

Extratemporal surgery is performed less frequently and the results are less impressive, with 50% becoming seizure free and 30% improved at 2 years. Dropping to about 30% by 10 years. The morbidity is related to the site of resection.

Hemispherectomy is particularly effective in controlling seizures, with approximately 80% becoming seizure free, but this operation is reserved for patients with a profound hemiplegia.

Corpus callosotomy results in 70% of patients having a worthwhile improvement, but less than 5% become seizure free.

Multiple subpial transection also results in a significant improvement of seizures in approximately 70%, but if eloquent cortex is involved there is at least a 20% chance of permanent neurological deficit.

Outcome of operation by pathology

The outcome of resective surgery is worse when no lesion can be identified by MRI (MRI-negative cases). When a lesion can be identified, the chance of operative success depends upon the pathology of the lesion, the site of the lesion, whether there are other associated abnormalities and whether the lesion can be completely excised. Also, the concordance of other pre-operative investigations is important. Thus, complete excision of well circumscribed benign tumours such as dysembryoplastic neuroepithelial tumours is associated with a 80–90% chance of excellent surgical outcome, while excision of focal cortical dysplasia is associated with 40–50% chance of success. Outcomes for cavernomas, low-grade gliomas and arteriovenous malformations tend to be somewhere in between. In some cases, there may be more than one pathology (e.g. temporal lobe tumour and hippocampal sclerosis). In many of these instances, surgical success is greater if both lesions are removed.

Vagal nerve stimulation and other stimulation devices

Vagal nerve stimulation is an approved device in the UK and is for the most part a palliative procedure. This approach involves surgically implanting a small stimulator under the skin in the neck, which intermittently stimulates the left vagal nerve. Recent data on the vagal nerve stimulator in patients with intractable partial seizures show a significant decrease in seizure frequency with few side effects. At best, vagal nerve stimulation offers approximately a 50% chance of a 50% or greater reduction in seizure frequency. The efficacy is comparable to short-term results in new antiepileptic drug (AED) trials. Few patients become seizure free, but there is some evidence of improved efficacy with time. More recently, VNS has an automatic stimulation mode, and will

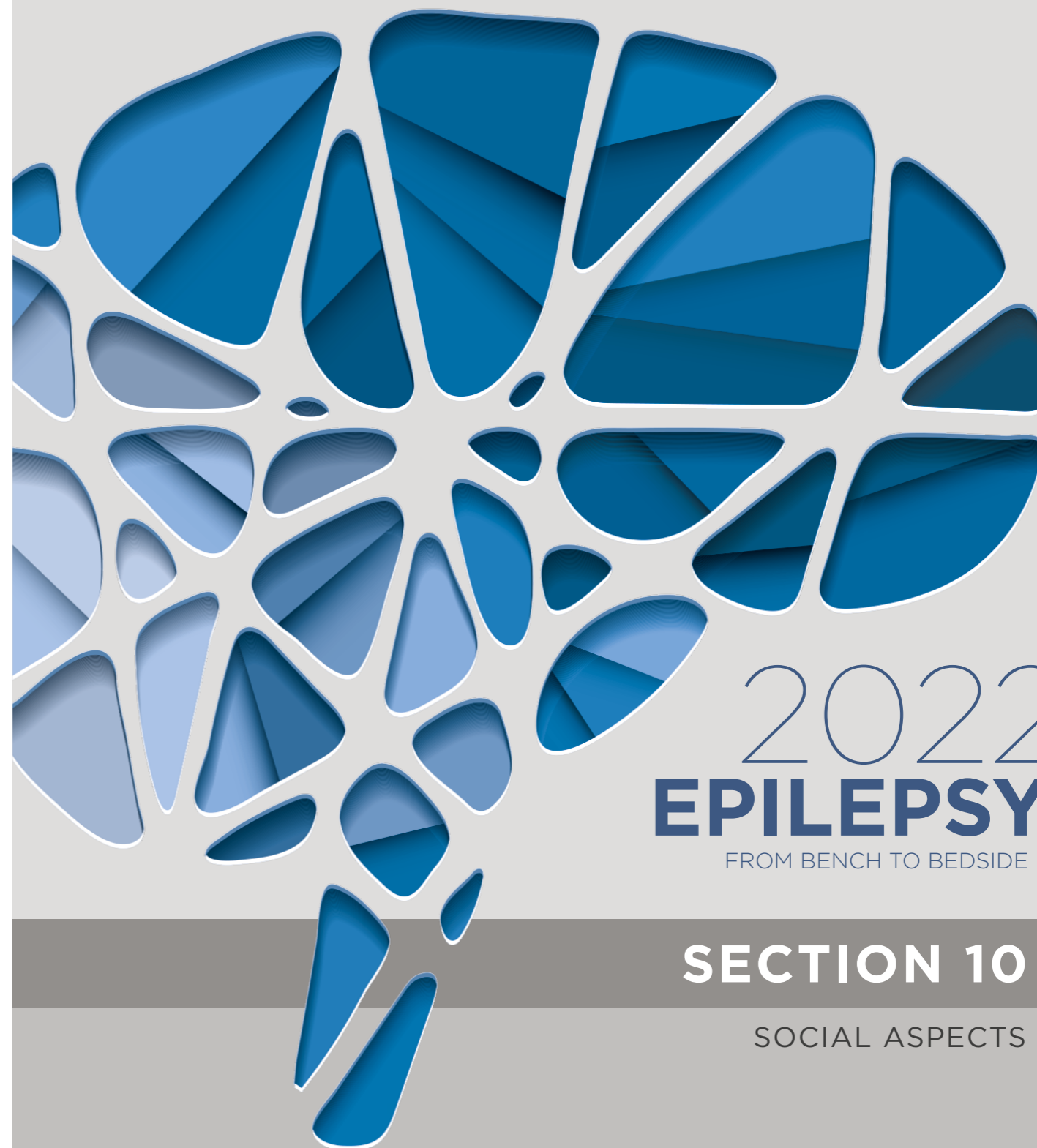
stimulate when it detects a rapid rise in heart rate (this is often associated with seizures). The main side effects are hoarse voice and pain. Peri-operative infections also occur, albeit uncommonly.

Trigeminal nerve stimulation is now licenced in Europe and this involves stimulation with external electrodes and stimulator over the first division of the trigeminal nerve at night – it is non-invasive but experience is limited. An external VNS stimulator is also available but experience is limited.

There is good evidence that deep brain stimulation, in particular of the anterior thalamic nucleus, can be effective in refractory epilepsy in which resective surgery is not possible. Experience in the UK is at present limited, but it has been shown to be effective in a randomised control trial with about 50% having a 50% reduction in seizures and more than 10% becoming seizure free. A closed-loop stimulation device (Responsive Neurostimulation System) that detects seizures and stimulates over the area from which the seizures arise is now also available (results from trials have been similar to other neurostimulation devices).

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 10

SOCIAL ASPECTS

CHAPTER 51

The patient's viewpoint

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Throughout the past century the management of epilepsy has greatly improved, with a wider choice of treatments aimed at specific types of seizures. The social and psychological consequences of living with epilepsy have in the past been relatively neglected, both in the clinical setting and by society in general.

Until relatively recently there was a lack of awareness of how a diagnosis of epilepsy could affect the patient. Where seizures remain refractory to treatment they may have a disturbing effect on the patient's life, inducing an understandable feeling of insecurity, which may affect self-esteem and confidence. Attacks may be frequent or infrequent, they may also happen in public, during the daytime, or at night when the patient is alone. Each possibility brings its own attendant fears.

Uncertainty about when the next attack may occur presents a particular problem. The patient's dilemma is living with an ever-present threat, never knowing when the next attack will happen. To the unaffected however, the person with epilepsy is 'normal' between attacks. These two very different perceptions illustrate the patient's dilemma, and it is easy to see how some patients feel isolated and misunderstood, perhaps leading them to live a rather covert type of existence.

When attacks occur in public a common source of anguish is the response of the onlooker who may:

- Recoil in horror if ignorant about the condition
- Make fun of the patient, covering their own embarrassment at the situation
- Ignore the patient, turning a 'blind eye'
- Panic and call an ambulance
- Intervene inappropriately (holding the patient down or introducing a hard object into the mouth).

The reaction of family and friends is key and family support and encouragement is important for positive adjustment over time. Epilepsy may affect family equilibrium and may be a frustrating disorder for everyone. An accurate understanding of the diagnosis is vital in family adjustment, as is containment of anxiety, if the patient is to have a good chance of learning to cope. A partner or family may be feeling:

- Grief for the patient
- Fears for their safety
- Doubts about their own ability to cope with the situation
- Resentment - disruption to their own lives
- Guilt - is it their fault?
- Isolation,

Where the patient is overprotected at home there is a real danger that this may lead to illness behaviour and increased dependency. A young adult may manifest difficulties in education, social and personal relationships and in the workplace.

The main tasks of the patient are to:

- Overcome social slights and negative remarks
- Have confirmation of his/her self-worth
- Adjust positively to the condition and integrate it into their lives
- Over time pursue an active social and working life.

Public misconceptions about epilepsy include:

- The association of epilepsy with mental illness and learning disability
- The assumption that single seizures cause damage
- The idea that epilepsy is inherited irrespective of cause
- The assumption that epilepsy is always for life.

It is important that these issues are introduced and discussed by the patient's physician at an early stage. Without proper information patients and their families are left to cope with unnecessary 'taboo' concepts, which add to their anxiety. The relative risks of disclosure and concealment may arise with interpersonal relationships and especially when seeking employment, where fear of rejection is marked.

In some countries, even today, people with epilepsy are not allowed to marry and are considered to be uneducable, unemployable and a danger to the community. In the UK many people still feel that revealing their condition will deter their employers who may view them as unreliable and likely to cause accidents. Some therefore decide to remain silent and live in fear of an attack and losing their job. A well-adjusted person should be able to tell anyone with whom they come in regular contact about their condition. Explanations should be kept simple and practical and public ignorance should not be assumed to be rejection.

Drug treatment for epilepsy may bring side effects causing problems for some patients. These may include:

- Fatigue and lassitude
- Poor memory
- Concentration difficulties
- Unsteadiness
- Nausea
- Weight gain or weight loss
- Mood or psychological changes.

These symptoms may be difficult to tolerate in the long term and alternate drug and treatment choices may be appropriate.

Refractory epilepsy means the patient will have to reassess how much risk is acceptable in order to live an integrated life. Each individual must decide what precautions are sensible in order to strike a reasonable balance between risk and precaution. Once a balance has been found, a patient may then maximise their potential and develop their talents.

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CHAPTER 52

Epilepsy clinic counselling

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The majority of patients seen at special epilepsy clinics have chronic, refractory epilepsy. As such, they represent a worse than average epilepsy group, some of whom may have special psychological and social problems.

The need for skilled counselling within this group, in addition to 'routine' therapeutic intervention, has been recognised. At the National Hospital for Neurology and Neurosurgery epilepsy clinics a special service is available to help address the problems commonly experienced by these patients and their families.

Refractory epilepsy may cause difficulty in a number of areas described in the previous chapter. Additional problems may arise in the patient's ability to cope with daily activities, accepting the diagnosis, and concordance with drug therapy offered. There may also be special problems which affect men or women and also with sexual relations.

Referrals

Patients who in the opinion of the medical team might benefit on clinical grounds and who live in the community (i.e. non-residential) may be referred for counselling. Referrals may be made by neurologists, neuropsychiatrists, general physicians, epilepsy nurse specialists and GPs. Patients may be referred from other hospitals and medical practices. Typical reasons for referrals include:

- Anxiety
- Depression
- Non-concordance with treatment
- Need for emotional support, psychosocial issues
- Advice and information about specific areas of living with epilepsy, e.g. women's issues, safety in the home, etc.

Common problems include:

- Perceived stigma
- Social isolation
- Low self-esteem
- Misconceptions about epilepsy
- Work/employment issues
- Anxiety and low mood.

The process

Patient motivation is key and must include an appreciation that success is dependent on equal effort by the counsellor and the patient. There should be consistency and the patient's reality should not be denied.

Patients are given an initial interview of one hour and may be offered regular follow-up sessions. A detailed history of the problems presented is taken and various options may be considered, depending on the counsellor's perception of the patient's ability to benefit from them. The patient is also screened for depressive symptoms and social behaviour patterns are observed.

In the early stages it is common for a patient to hold negative beliefs which may block progress. These commonly include:

- I will never make it
- There is no point in trying
- Others will reject/dislike me
- I have no control over my life.

Time is important when addressing such issues as fear, anger, denial and confusion. Many fears arise out of public misconceptions about epilepsy which may be allayed with proper information, together with support and reassurance.

The health professional's actions are to:

- Identify problems
- Offer coping strategies
- Overcome blocks to change
- Set and review agreed tasks.

Coping strategies are important in epilepsy counselling. They enable the patient to deal with his or her problems in a particular way. Once it is understood that choices are available, the patient may explore these options with the counsellor. In time, a more balanced view of the potential intrusion of epilepsy into everyday life may be achieved and general anxiety levels lowered as the patient feels more in control.

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CHAPTER 53

Counselling for epilepsy surgery

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Surgery is considered for people with epilepsy whose seizures are not well controlled by antiepileptic medication, or who continue to experience unacceptable side effects for whom the possibility of surgery has been raised.

A number of different factors need to be taken into consideration before it is possible to say whether or not a patient may benefit from surgical treatment. In the majority of cases, surgery will normally be considered if:

- Antiepileptic drug (AED) treatment has been tried using a number of different medications but these have proved unsuitable, or unsuccessful in stopping the patient's seizures
- The epilepsy can be seen to be arising from one localised area of the brain
- The part of the brain causing seizures is accessible to the surgeon and can be removed without damaging other parts of the brain or brain functions, such as speech, sight, movement or hearing
- The patient has no other medical problems which would make them unsuitable for this type of surgery
- The patient is thought to have a good chance of becoming seizure free following the surgery or having a worthwhile improvement in severity, frequency or both.

Referrals

At the National Hospital for Neurology and Neurosurgery, a dedicated epilepsy surgical counselling service exists in which all patients are seen prior to surgery. The purpose of this is to enable the patient and their family to discuss any concerns they may have and to clear up areas of misunderstanding prior to making the final decision as to whether or not to go ahead with an operation. The surgical counsellor is seen towards the end of the pre-operative investigations and referral may come from either the patient's consultant neurologist or neurosurgeon.

The health professionals have the report of the consultant neurologist or neurosurgeon to hand and will be able to advise about the patient's individual case. At this time, it is important to find out more about the patient's social support and family circumstances which vary from case to case. The planning of professional support in advance of the operation is important in patients who do not have this support at home.

Expectations of surgery

Expectations of surgery vary a great deal. This is an issue that needs to be discussed in detail with individual patients in order to find out how seizures have impacted on their lives so far and what they may reasonably expect from themselves and others if the operation is successful. Common areas for misunderstanding include:

- What the patient should do prior to going into hospital
- The length of the stay in hospital
- What happens prior to the operation
- The amount of the patient's hair to be shaved prior to surgery
- The reason for the admission to the intensive therapy unit (ITU) immediately after surgery
- How the patient will feel when they wake up
- How soon they may be visited.

Some patients may receive financial benefits prior to surgery and it is important to discuss what might happen if the operation were successful and the patient became seizure free. As with all benefits, it is incumbent on the patient to report any change in circumstances, including improvements in their health, that might affect their right to benefits, or the amount of benefit they receive. Thus, when considering surgery, it is important that the patient is made aware of this and the possible responsibility they would face if the operation were to be completely successful. The counsellor would point out that a time may come when the patient would no longer be considered disabled and therefore not qualify for the benefit that they may have been receiving.

It is very important to have a plan that goes beyond successful surgery and to take into account what the patient plans to do with their life in a number of ways. The counsellor may advise on useful organisations for the patient to contact for help with training, finding employment and general advice on grants, courses and access to education.

Practical advice

The health professional will also discuss such issues as care of the wound following surgery, recuperation at home, how soon the patient may expect to resume a variety of activities and how long the effect of the anaesthetic may be expected to take to wear off.

Other areas of discussion commonly include:

- The importance of staying on their medication
- How soon can the patient do sport or vigorous exercise after surgery
- When the patient can have sex after surgery
- Who to contact in the case of medical problems during recuperation
- When the patient will be seen again by the surgeon, neurologist and psychiatrist
- Driving and the DVLA regulations
- How soon the patient may travel following surgery
- General advice on recuperation.

It is important for the patient to realise that losing their seizures may sometimes lead to other problems and stresses in daily life and that this is one of the reasons for continued contact with the hospital, neurologist, psychiatrist and psychologist for some time after discharge.

Common emotional problems after surgery

Patients need to understand that it is common to see mood swings and a combination of anxiety and depression in 20-30% of people who have epilepsy surgery. This may be distressing and cause tiredness, loss of sleep, and poor appetite and make the patient feel on edge. Symptoms may resolve on their own in about 4-6 weeks, although some patients may need antidepressant medication or counselling. About 10% of people may go on to develop a more significant form of depression, with sustained mood changes and negative thoughts about the world and their future. This may require more formal support including antidepressants and/or counselling. Admission to hospital is rarely required. A minority of patients may develop a psychosis post-surgically. Relatives are counselled that if they notice a difference in the patient's mood causing concern they should report it to the clinician concerned.

It is important that the patient appreciates that antiepileptic medication needs to be continued after surgery. The counsellor will ensure that the patient understands that no changes in medication will normally be made for the first 12 months and the aims of surgery will normally have been achieved within two years.

CHAPTER 54

Employment

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People with epilepsy have been shown to be up to twice as likely as people without it to be at risk of unemployment¹; and as being also subject to underemployment, relative to the level of their skills and qualifications²; with related impacts for their financial status and psychological well-being. Factors contributing to the likelihood of under- and unemployment in people with epilepsy are both internal and external. In the former category, a range of clinical factors have been demonstrated as predictive of employment status, including seizure frequency and type, age of onset of epilepsy and duration, and the adverse cognitive effects of antiepileptic drugs (AEDs); and the effects of these clinical factors may be further compounded by internal psychological factors, for example, reduced self-esteem and achievement expectations³. External mechanisms, in the form of stigma and discrimination⁴, which may be either formal or informal, overt or covert, intentional or unintentional, also contribute to the compromised employment position of people with epilepsy; and their effects may be felt particularly hard in areas or times of high unemployment. For many people with epilepsy, employment is the major quality of life issue facing them^{5,6}.

The question of employment is crucial when considering the needs of people with epilepsy. Working, being an employee and earning a living, is an outward indication of integration and acceptance by others in society. The advent of seizures can have serious effects on work prospects and as a consequence can adversely influence psychosocial functioning of the person with epilepsy, and his or her family. In most surveys of people with epilepsy, employment problems are frequently highlighted^{7,8}. From a societal viewpoint the economic cost of epilepsy in the workplace is also a concern. A recent study suggested that of the estimated 200,000 people with epilepsy of working age in the UK as many as half are experiencing moderate or severe problems with employment⁹. Employment was the third major concern cited by people with epilepsy after driving and medication in a survey conducted by Epilepsy Action, with a third of respondents describing the problem as serious.

Employment problems

Restrictions

There are a number of ways in which epilepsy can have an impact on employment. In the first instance certain occupations are barred by law to the person with epilepsy because of the potential hazards to him or her or others if a seizure occurs in the workplace. These include working as an aircraft pilot, ambulance driver, merchant seaman, taxi driver, train driver, and in the armed services. Secondly, the stigma attached to epilepsy and the resulting prejudice on the part of the employers and co-workers limits employment opportunities for individuals with epilepsy. Thirdly, there are also some occupations in which difficulties may be experienced, although there are no statutory barriers concerning them, such as teaching posts involving physical education, science and technology in state schools, some nursing posts, work with young children and jobs in the prison service involving close contact with inmates. Certain positions also involve substantial risks

if seizures are not fully controlled and therefore should not be recommended. These include working at heights and working alone near open water or around unguarded machinery or fires. To hold a Large Goods Vehicle (LGV) or Passenger Carrying Vehicle (PCV) driving licence, an individual must have suffered no seizures or had no treatment for seizures for ten years (see Chapter 54). However, regulations can change so it is important to make sure information is up to date.

Unemployment

Quoted unemployment rates vary widely. Figures cited for vocationally active people with epilepsy are at least twice that of the general population. Elwes and co-authors reported an unemployment rate of 46% for people with epilepsy, as opposed to 19% for a control group¹⁰. Significantly longer periods of unemployment and higher rates of early retirement are also reported. When epilepsy is well controlled, or seizures are nocturnal, it has much less impact on employment rates and history. Rates of underemployment are reported to be higher for people with epilepsy but these rates are more difficult to quantify. However, the majority of studies investigating employment and unemployment rates among people with epilepsy have been based on highly selected populations or small samples. In a 1995 study by Jacoby on a large cohort of people with relatively well controlled epilepsy, 71% of those of working age were in employment with 26% unemployed but for reasons other than epilepsy and only 3% citing epilepsy as the reason for not working¹¹. A breakdown of employment rates by clinical and demographic factors is displayed in Table 1.

Table 1. Influence of demographic and clinical characteristics on current employment status.

	% Currently employed	Number of patients
Sex		
Male	79	213
Female	64	266
Age at which first education completed		
<16	67	340
17+	81	139
Epilepsy was		
Active	65	121
In remission	73	348
Currently taking AEDs		
Yes	67	355
No	70	139
Self-assessed health status		
Excellent/good	75	398
Fair/poor	49	79
Neurological deficit		
Yes	70	406
No	71	73
Seizure type		
Partial	53	32
Partial with secondary generalised	74	160
Generalised	70	286

Reproduced with permission from Jacoby 1995¹¹

Work performance

Assessing productivity is difficult as there is no agreed definition or means of testing it. To obtain data on the effects of epilepsy, comparisons should ideally be made with a person who does not have epilepsy performing the same task. The available evidence does not suggest any striking lack of efficiency at work in employees with epilepsy. One study of an electrical components firm recorded reduced working speed but this was reported to be associated with an increase in precision, which was considered a positive outcome.

Data on absenteeism do not indicate any markedly elevated rates in people with epilepsy and turnover rate has been reported as lower. This may be due to anticipated or real difficulties in obtaining another job.

Seizures at work

If a seizure does occur at work, three factors affect the level of disruption: the severity, the suddenness and the location. A severe seizure at work is likely to cause a good deal of disturbance and disruption, at least to those in the immediate vicinity. Milder attacks cause little disturbance and may even go unnoticed. Possibly the most disruptive seizures are those which occur without warning or in someone who was not known to have epilepsy.

Stress

Stress is recognised as a possible seizure precipitant. Reports in the literature suggest that the person with epilepsy may be particularly vulnerable during the first few weeks of a new job. At this time people who are keen to prove their worth and make a good impression may put themselves under the kind of stress that makes seizures likely to occur, particularly if they have not disclosed their epilepsy. It has also been reported from a US survey that as many as 80% of people with epilepsy regarded the fear of having a seizure at work as a reason for not seeking or maintaining open employment.

Shift work

It has been suggested that adapting to shift work will increase the chances of suffering a seizure in people with epilepsy who may be particularly susceptible to persistent fatigue, sleep disturbance and disruption of routine. If a patient has more seizures in the context of lack of sleep or occasional missed doses of medication then they might be vulnerable if they undertake shift work, as might individuals with well established nocturnal seizures.

Working with computers

For the majority of people with epilepsy, working in front of a computer monitor will not be a problem and will not trigger seizures. Individuals with photosensitive epilepsy are at risk, however this is a rare condition in adults with seizures. Most computers work at a frequency which does not tend to provoke seizures. Laptop computers are even less likely to trigger seizures than ordinary computers. Work involving computers has increased dramatically in recent years and this growth is of potential benefit to people with epilepsy. Working with computers is relatively safe and enables employment within the home, which can overcome the problems of transport.

Accidents at work

The few studies looking at the experience of people with epilepsy at work tend to show that they have no more accidents at work than anyone else. Of course, this may be because they are less exposed to potentially high-risk situations, such as working at heights or driving vehicles. It may also be that when accidents occur, particularly if they are relatively minor, they are less likely to be reported. In one study of a sheltered workshop employing people with epilepsy, the accident rate was considered so impressively low that the company was awarded insurance premium reductions. In most work situations it should be possible to minimise the risk of accidents.

Employees accident liability

The ineligibility of people with disabilities for employees' accident liability insurance has been used incorrectly as a reason for not employing someone with epilepsy. Employers are obliged to take out insurance to cover injury that might arise from work. The majority of insurance policies will treat anyone with a disability on the same terms as the rest of the workforce providing that the duties allocated take the disability into account. To ensure they are covered employers may need to seek expert advice. In the UK this can be obtained from Health and Safety Executives and the Employment Medical Advisory Service.

Pension schemes

Many employers may believe that new recruits to their pension schemes should have high standards of health. This is not the case, however. If a person is suitable for employment then they are suitable for a pension scheme. Large company schemes are usually based on a group policy with no requirement for individual health criteria to be met.

Disclosure

Many people with epilepsy choose not to declare their epilepsy to their existing or prospective employers. Those who are more likely to have seizures during the working day are more likely to declare it than those whose epilepsy is in remission or occurs during sleep. The Health and Safety at Work Act (1974) requires that both employers and employees declare factors which might prejudice the safety of employees and epilepsy is regarded as a relevant factor. A failure to declare can result in instant dismissal which would not be considered unfair if brought before an industrial tribunal.

Overcoming employment disadvantages

Legislation

Some protection from discrimination in employment is afforded by legislation which stipulates that people with disabilities are given equal rights to employment. In 1995, in line with several other European countries, the Disabilities Discrimination Act was introduced in the UK. It is too soon to judge what impact this will have on recruitment but similar legislation in the US has been successfully tested in the courts by people with epilepsy. Shortcomings of this legislation for people with epilepsy have recently been highlighted¹².

Adequate assessment

When assessing employment prospects, many factors need to be considered. Too often, most focus is placed on seizure-related factors. While the timing, frequency and nature of attacks is important, these may actually not be the most relevant. A person's skills, qualifications and work experience will be crucial. In addition, some inquiry into a person's understanding and attitude toward his or her epilepsy may be helpful. A prospective employee's ability to present his or her own seizures in an appropriate and reassuring way can do much to allay the employer's concerns.

Difficulties obtaining relevant qualifications or maintaining employment may reflect an underlying cognitive difficulty. A thorough neuropsychological assessment may help to identify any problems that may be amenable to intervention, perhaps via a change in medication, which should be taken into account when advising on career options.

Training, counselling and placement

Unrealistic employment aspirations can be prevented by accurate guidance concerning career options. Counselling and training is vital to provide input on job presentation skills and the role of psychosocial factors. Most people with epilepsy do not have access to specialist epilepsy rehabilitation services and must rely on mainstream resources. Existing research indicates that

employment training schemes aimed specifically at people with epilepsy generally achieve better results than more generic schemes. Components of these programmes include neuropsychological assessment, vocational training, interview techniques (including disclosure) and specialist placement and post-placement programmes.

Table 2. Principles for employing a person with epilepsy: good seizure control, work-related aptitudes and skills and a positive approach to epilepsy are key factors in determining a person's employability.

Health care

When assessing an employee or job applicant, the employer needs to understand some of the basic facts about epilepsy and its possible impact on work performance:

- Seizures can take many forms and many people have only one seizure in their lives - in such cases a diagnosis of epilepsy is not usually made
- When a seizure occurs for the first time there may be a detrimental effect on self-confidence and the person may require psychological support and education about epilepsy
- In most cases recurrent seizures can be controlled completely with drug treatment
- If prescribed properly, drugs for epilepsy should not produce side effects that have a noticeable effect on work performance
- In such cases, assessment by a physician expert in epilepsy will often improve seizure control and reduce side effects
- Employees with epilepsy should be provided with the same health and accident insurance cover as other employees

Job suitability

The vast majority of jobs are suitable for people with epilepsy:

- When medical advice is sought about the suitability of particular jobs for people with epilepsy, the guidance given should take into account the known facts about epilepsy and seizures - blanket prohibitions should be avoided
- In those jobs known to carry a high physical risk to the individual worker or to others, the way the work practice is organised should be examined to reduce this risk to an acceptable level
- Only in those situations where this cannot be done are restrictions on the employment of people with epilepsy justified
- When a person with epilepsy possesses the right qualifications and experience, job suitability should be assumed

(Continued)

Table 2. (Continued)

Recruitment and selection

- When personal health information is required it should be processed separately from the job application form and evaluated by a suitably qualified person
- Interviews should focus on the capabilities of the individual and not on his or her real or assumed limitations
- Suitability for a particular job should be decided by the employer before any implications arising from the job applicant's epilepsy are considered
- If a medical opinion is sought, the guidance should be based on knowledge of the particular job and details of the individual's epilepsy

Assistance at work

When an employee has seizures for the first time, the employer should respond fairly by giving the employee adequate opportunity to receive proper medical treatment before making any decisions about job suitability:

- If seizures are likely to occur at work, the employer should help the employee with epilepsy to disclose the epilepsy to work colleagues
- Some first-aid training or other information should be provided to those who might be involved should a seizure occur
- If any special job restrictions are needed there should be clearly stated policies about how they are to be implemented, reviewed, or lifted, in terms of set time periods
- If, despite proper medical attention, redeployment to another job is necessary, appropriate counselling and vocational guidance and if necessary rehabilitation services should be made available at an early stage

Educating employers

Negative attitudes regarding the employment of people with epilepsy is often the result of ignorance. Much can be accomplished by educating employers. To this end the Employment Commission of the International Bureau for Epilepsy has drawn up a set of principles aimed at employers to improve awareness and hopefully employment practice. Attention is drawn to four key areas: health care, job suitability, recruitment, and selection and assistance at work. An adaptation of the Commission's Principles are presented in Table 2.

Summary

Employment serves a number of important functions, including providing a sense of self-worth, an identity and personal status. Being unemployed contributes to emotional and behavioural problems and is considered as a major source of stress and a contributory factor to increased psychopathology in people with epilepsy¹¹. A number of studies have highlighted that rates of employment are lower in people with epilepsy than those without, however, more recent findings

have suggested that rates will vary by clinical and demographic characteristics. For example, people with well controlled epilepsy and those in remission have employment rates similar to those of the general population without epilepsy⁶. Smeets and colleagues¹² have recently provided a conceptual overview of the employment barriers experienced by people with epilepsy. The authors conclude that there is a need for specific vocational rehabilitation that focuses on increasing self-efficacy and coping skills. However they also recognise the need for longitudinal research to demonstrate that employment opportunities can indeed be improved through specified vocational rehabilitation interventions.

Jacoby, Gorry and Baker¹³ have recently argued that the need for continuing education of employers of people with epilepsy is self-evident. However, according to the authors 'education alone is not enough: the problem of bridging the gap between knowledge and attitudes and behaviour also needs to be addressed though exposure of persons without disabilities to those with them.'

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CHAPTER 55

Driving

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Obtaining a licence to drive is subject to legislation. The regulations are necessary because there is a higher rate of road traffic accidents and accidental deaths in drivers suffering from epilepsy¹⁻⁵. For this reason, obtaining a licence to drive is subject to legislation in most countries. Legislation needs to balance the excess risks of driving against the social and psychological disadvantage to individuals of prohibiting driving. The following outlines the regulations, and mechanisms for applying these, in the United Kingdom, and is based on documentation provided by the licensing authority and the Epilepsy Society websites.

In the UK, the Driving and Vehicle Licensing Agency (DVLA) and in Northern Ireland the DVLNI, have medical departments which, on behalf of the Secretary of State, are empowered to consider the medical history of a licence applicant/holder and can, with the applicant's consent, obtain medical details from an applicant's hospital doctor or general practitioner. The DVLA, and not the patient's personal medical advisors, make the decisions to allow/bar licensing. This arrangement, not shared by most other countries, has the important advantages that the medical aspects of the doctor-patient relationship are not overly compromised by questions of driving and that the personal doctors are not liable for the consequences.

DVLA regulations and guidance change, so consult the latest version of the DVLA guidance on the internet at:

<https://www.gov.uk/guidance/assessing-fitness-to-drive-a-guide-for-medical-professionals>

For neurological conditions, consult:

<https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive>

Synopsis of current regulations

Group 1 includes motor cars and motor cycles.

Group 2 includes large lorries (category C) and buses (category D). The medical standards for Group 2 drivers are stricter than those for Group 1 because of the size of the vehicles and the higher risk entailed by the length of time the driver may spend at the wheel in the course of his/her occupation.

All drivers who obtained entitlement to Group 1, category B (motor car) before 1 January 1997 have additional entitlement to category C1 and D1. C1 is a medium size lorry of weight between 3.5 and 7.5 tonnes. D1 is a minibus of between 9 and 16 seats, not for hire or reward. Holders of C1 and D1 entitlement retain the entitlement until their licence expires or it is medically revoked.

On subsequent renewal the higher medical standards applicable to Group 2 will apply. Under certain circumstances volunteer drivers can drive a minibus of up to 16 seats without having to obtain category D1 entitlement. Individuals should consult DVLA for a detailed fact sheet.

Epilepsy is a ‘prescribed disability’, which means that an individual with epilepsy is barred from holding a licence, unless the following criteria concerned with the control of seizures are met:

Group 1 licences (motorcars, vans and motorcycles)

An applicant for a licence suffering from epilepsy shall satisfy the following conditions:

- a. They shall have been free of any epileptic attack during the period of one year immediately preceding the date when the licence is granted: or
- b. Asleep seizures with no history of awake seizures. If the individual has only **ever** had asleep seizures then once this pattern of only asleep seizures has been established for **one year**, they can apply for a new Group 1 licence to drive, even if asleep seizures continue. If awake seizures have occurred in the past, but seizures now only occur during sleep, a licence is permitted if the applicant has had seizures only during sleep for three or more years.
- c. The driving of a vehicle is not likely to be a source of danger to the public.
- d. Seizures which do not affect consciousness or ability to control a vehicle. An individual can apply for a new Group 1 licence after one year of not driving, even if they are still having seizures **if all of the following apply**:
 - they stay fully conscious during the seizures
 - they would be able to act, react, and control a vehicle normally during the seizure
 - they have **only** these types of seizures and no other type, and
 - they have never had a seizure that affects consciousness or ability to control a vehicle. This liberalisation does not apply, therefore, to individuals who have had epilepsy surgery for focal seizures with loss of awareness, and who continue to have auras following surgery.
- e. A driving licence is restored after six months if a seizure is precipitated by a medically-advised drug change, if this change is reversed. The previously effective medication needs to have been reinstated for at least six months. An exception to this is a breakthrough seizure that does not affect consciousness or ability to drive, or that is an asleep seizure (see above). The individual still needs to tell the DVLA about the seizure but may be allowed to drive and not lose their licence, depending on the types of seizures they have had previously.

The following circumstances commonly arise:

Single unprovoked seizures. These are not considered as ‘epilepsy’ by the DVLA unless a continuing liability can be demonstrated. The default for the licensing authority is to prohibit driving for a 12-month period after the attack. Driving privileges, however, may be restored after six months with the support of a neurologist and if MRI scan and EEG do not indicate a high risk of seizure recurrence.

Provoked seizures. If a seizure is considered to be ‘provoked’ by an exceptional condition which will not recur, epilepsy (defined as a condition with a continuing liability to seizures) is not deemed to be

present. Driving is usually allowed once the provoking factor has been successfully or appropriately treated, and provided that a ‘continuing liability’ to seizures is not also present. These cases are treated on an individual basis by the DVLA. In general, a Group 1 driving licence is suspended for 6 months after a provoked seizure, if there is not deemed to be an increased risk of further seizures occurring. If there are risk factors for further seizures, such as if there is a prior history of epilepsy, a driving licence will be suspended until the individual has been clear of all seizures for 12 months.

A cautious attitude to ‘provocation’ is taken, however, and the provoking factor must be exceptional. Seizures related to alcohol or illicit drugs are not considered ‘provoked’.

In the absence of any previous seizure history or previous cerebral pathology, the following seizures may also be regarded as provoked:

- eclamptic seizures
- reflex anoxic seizures
- seizure in first week following a head injury
- at the time of a stroke/TIA or within the ensuing 24 hours
- during intracranial surgery or in the ensuing 24 hours

A convulsive seizure occurring at the time of impact of a head injury is regarded as a “concussive convulsion” and not associated with an increased risk of subsequent seizures. In consequence, driving privileges are not affected. Seizures occurring during an acute exacerbation of multiple sclerosis or migraine will be assessed on an individual basis by DVLA.

Electroencephalographic changes. Although EEG can provide useful confirmation of epilepsy and its type, the diagnosis of epilepsy is essentially clinical. Episodes of 3 Hz spike/wave discharges in idiopathic generalised epilepsy and electrographic seizures are not a bar to driving if there is no clinical accompaniment.

Neurosurgery. When epileptic seizures occur following neurosurgery, the epilepsy regulations must be applied. An exception can be made when seizures occur at the time of surgery. Following intracranial surgery, even if seizures have not occurred, driving is usually prohibited for a period which varies according to the type of underlying pathology, and the nature and site of the neurosurgery. The duration of the period of restriction is based on the risk of seizures.

Cerebral lesions. When certain cerebral lesions are demonstrated, a single seizure is considered to be epilepsy (on the basis that a continuing liability to seizures is present). In the following conditions, even when epilepsy has not occurred, restrictions are applied because of the known risk of epilepsy: malignant brain tumours, cerebrovascular disease, serious head injury, intracranial haemorrhage and cerebral infection. The duration of the period of restriction is based on the risks of seizures developing.

Treatment status. The epilepsy regulations apply whether or not the patient is receiving antiepileptic drugs (AEDs). Starting, or changing, AED treatment does not influence a decision about licensing. If antiepileptic medication is being completely withdrawn in a person with epilepsy who has been seizure free for some years and who has a Group 1 licence, the DVLA recommend that the individual does not drive during the tapering of the AED or the subsequent six months, as this is the period with the highest risk of seizure recurrence.

Obligations. There is a legal obligation for the individual with epilepsy to inform the DVLA about their condition. This is the case regardless of clinical or domestic circumstances or extenuating factors. The obligation on the doctor is to inform the patient about the regulations and their

requirement to inform the DVLA. This advice should be recorded in the medical notes, to avoid claims of negligence.

If an individual is known to be continuing to drive it is recommended to repeat the advice in the presence of their relatives, and to point out that their insurance policy would be invalid. If that individual is known to be continuing to drive it is appropriate to inform the DVLA, and advisable to tell the individual that you are doing this as the needs of public safety outweigh the needs of medical confidentiality. It is sensible to inform the medical indemnity organisation and the GMC that you are taking this course and the reasons for your decision.

Withdrawal of AED on medical advice. From a medico-legal point of view, the risk of further epileptic seizures occurring during this therapeutic procedure should be noted. If an epileptic seizure does occur, the patient will need to satisfy driving licence regulations before resuming driving and will need to be advised accordingly. It is recognised that AED withdrawal is associated with an increased risk of seizure recurrence. A number of studies have shown this, including the Medical Research Council Antiepileptic Drug Withdrawal Study Group that found a 40% risk of seizure recurrence on withdrawal of medication. More recently the “timetostop” study has an online tool (below link) for assessing relapse risk after paediatric epilepsy surgery.⁶

www.epilepsypredictiontools.info/ttswithdrawal

The Secretary of State's Honorary Medical Advisory Panel on Driving and Disorders of the Nervous System has recommended that patients should be warned of the risk they run, both of losing their driving licence and also of having a seizure which could result in a road traffic accident. The Panel advises that patients should be advised not to drive from commencement of the period of withdrawal and thereafter for a period of six months after cessation of treatment.

Group 2 licences (lorries larger than 3.5 tonnes and passenger carrying vehicles of nine seats or more for hire or reward)

An applicant for a licence shall satisfy the following conditions:

- a. No epileptic attacks have occurred in the preceding ten years and that the individual has taken no AED treatment during this period.
- b. There is no continuing liability to epileptic seizures.

The purpose of the second condition is to exclude persons from driving (whether or not epileptic seizures have actually occurred in the past) who have a potentially epileptogenic cerebral lesion or who have had a craniotomy or complicated head injury, for instance.

If a Group 2 licence holder has an episode of loss of awareness of uncertain cause, but which is not diagnosed as being due to epilepsy, their licence will be suspended for five years.

After an isolated or provoked epileptic seizure, a Group 2 licence is suspended, and may be reinstated after five years if no AEDs have been taken to control epilepsy.

The Secretary of State may require an appropriate medical assessment by a neurologist; and be satisfied that the driving of a vehicle by the applicant, in accordance with the licence, is not likely to be a source of danger to the public.

Taxis, ambulances or emergency service vehicles

The DVLA does not issue licences for taxis, ambulances or emergency service vehicles. It is recommended that Group 2 medical standards should be applied.

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Useful addresses:

The Medical Adviser
 Drivers' Medical Group
 DVLA
 Longview Road
 Morriston
 SWANSEA
 SA99 1TU

Driver and Vehicle Licensing
 Northern Ireland
 County Hall
 Castlerock Road
 COLERAINE
 BT51 3TB
 Northern Ireland

Tel: 01792 782337 (medical professionals only) Tel: 028 703 41369
 Email: medadviser@dvla.gsi.gov.uk
 (medical professionals only)

CHAPTER 56

Medico-legal aspects of epilepsy

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Epilepsy and the criminal law

Everyone who has reached the age of discretion is, unless proven to the contrary, presumed by law to be sane and to be accountable for his actions. This is the doctrine of *mens rea*. 'Actus non facit reum nisi mens sit rea' - the deed does not make a man guilty unless his mind is guilty. To make a man liable to imprisonment for an offence that he does not know he is committing, and is unable to prevent, goes against the spirit of English justice.

Unless the offence is a statutory one which carries an absolute liability (e.g. driving with a raised blood alcohol level), the doctrine of *mens rea*, or the presence of a guilty mind, can only be negated by six major considerations: (1) the person is defending themselves; (2) the person was under duress; (3) the person was provoked; (4) that the mind is not guilty because it is innocent; (5) because the mind is diseased; (6) because at the time of the act there was an absence of mind.

The defence of innocence is seldom used and is sometimes applied to mental subnormality.

The defence of Disease of the mind can only be used by patients with epilepsy who, at the time they commit an offence, have an associated mental illness, for example, either a post-ictal or an inter-ictal paranoid psychosis and who at the time they commit their crime are suffering from an insane delusion. In these circumstances, epilepsy is very little different from any other functional psychotic illness and the rules applying to persons with epilepsy are no different from those applying to the mentally ill population as a whole.

The law relating to epilepsy is, however, distinct for the sixth category of defect - that no mind was present at the time of the act - for it can be claimed that during an epileptic seizure the mind is absent and so any action carried out is automatic. In law, this defence is the defence of automatism. An act carried out in the absence of mind is known legally as an automatic act, and the defendant may wish to establish the defence of automatism. The legal and medical definitions of automatism are different. This may be more clearly understood if it is recognised that the law has to deal with the protection of the public as well as the rights of the individual, and is not overly concerned with the brain and its mechanisms. Medicine, on the other hand, is concerned primarily with brain mechanisms, their disorder and cure, and is not unduly concerned with the rights of society and the protection of one individual from another.

Automatism

An epileptic automatism is defined medically as:

'A state of clouding of consciousness which occurs during or immediately after a seizure, during

which the individual performs simple or complex movements without being aware of what is happening. The impairment of awareness varies. By this definition, automatisms are really very common, and can be divided into two groups: ictal automatisms, which occur during a seizure, and post-ictal automatisms, which occur after a fit.seizure.

The accepted legal definition of automatism is:

‘The state of a person who, though capable of action, is not conscious of what he is doing ... it means unconscious, involuntary action and it is a defence because the mind does not go with what is being done.’

This definition is very close to the medical definition, and it would thus seem that doctors and lawyers are in agreement about what constitutes an automatism. The law, however, defines two types of automatisms: sane (automatism simpliciter), e.g. after a head injury, and insane (automatism due to disease of the mind), e.g. resulting from arteriosclerosis in the brain. Either kind of automatism can be put forward as a defence and if accepted by the court will enable the defendant to plead not guilty. However, the consequences of a successful defence are quite different in the two cases. In the case of sane automatism, the defendant will walk free from the court. But in the case of an insane automatism the defendant will be sentenced under the Fitness to Plead and Insanity Act 1991. This Act allows the judge to decide on disposal, which can range from allowing the defendant to go free to the detention of the defendant in a secure mental hospital for an indefinite period at the discretion of the Home Secretary.

The present standing of the difference between sane and insane automatism is as follows: Automatism simpliciter occurs when the mind is disordered by an external factor such as an injection of insulin, a blow on the head, the injection of an anaesthetic or even a reflex action resulting from a bee sting. An insane automatism occurs when the mind is disordered due to an intrinsic factor which leads to a situation that is prone to recur and may result in violence. Thus any organic condition of the brain or the body resulting in a disorder of the mind, even if temporary, is an insane automatism. Automatic acts carried out during sleep, during dissociated states, and during any psychiatric or medical condition causing a disruption of brain function which is due to an internal condition is now insanity. This leads to differences such as, for a violent act committed while the mind is disordered due to an excess of insulin is automatism simpliciter if the insulin is injected, while it is an insane automatism if the insulin comes from an insulinoma of the pancreas.

Epilepsy and criminality

Not infrequently, psychiatrists and neurologists are called upon to decide whether or not a crime has been committed during an epileptic seizure, and whether or not the defence of automatism is one that can be substantiated by the medical facts of the case¹. Usually the offence is fairly trivial, for example, shoplifting during either a post-ictal confusional state or during the automatism of a complex partial seizure. Occasionally, however, defendants may claim the defence of epileptic automatism when there is little evidence to support this. The physician should satisfy themselves on the following six points before going to court to substantiate the diagnosis of epileptic automatism:

1. The patient should have a previous diagnosis of epilepsy. It is clearly unlikely that a crime will be committed during a first seizure. Thus, unless there is overwhelming evidence, the diagnosis of epilepsy should be rejected if the act is said to have occurred during a first seizure. The case of epilepsy is strengthened if there is evidence that the patient is either subject to ictal or post-ictal automatisms, and that the behaviour described during the crime is consistent with behaviour that has been previously described during such an automatism and documented.

2. The act should be out of character for the individual and inappropriate for the circumstances. Clearly, if the defendant is habitually aggressive and commits a violent and aggressive crime, it is much more difficult to substantiate the diagnosis of epileptic automatism than if the act occurs in a patient who is mild mannered and tolerant. It is also important that the act should be inappropriate in the circumstances in which it occurred. A violent act of automatism during a fight at a football match, although it may occur, is less likely to persuade the court than one which occurs during a Sunday stroll.
3. There must be no evidence of premeditation or concealment. An epileptic automatism must arise *de novo* from ongoing behaviour. If there is any suggestion that there was preplanning for the act, then it is not possible to substantiate the diagnosis of automatism. Concealment is also unlikely after an automatism. On regaining consciousness, a patient emerges from a state of confusion or amnesia and is thus unlikely to register the full meaning of the events which have occurred. His natural response to such a situation is immediately to seek help, and not to conceal the evidence of any crime.
4. If a witness is available, they should report a disorder of consciousness at the time of the act. Unfortunately, witnesses are not always available, but when they are, detailed questioning about the defendant's behaviour to establish a disorder of consciousness is essential. Features to seek are those of automatism: staring eyes, a glassy look, stereotyped movements, confusion and evidence that the person was out of touch with his surroundings.
5. Because the act occurs during an automatism or post-ictal confusional state, a disorder of memory is the rule. It is unlikely that an epileptic automatism can occur in the setting of clear consciousness. Thus, memory for the act should be impaired. It is essential that there is no loss of memory antedating the event. During a seizure, loss of memory starts with the onset of the seizure and not before it. Thus any loss of memory which antedates the episode is a point against it being an epileptic automatism.
6. The diagnosis of automatism is a clinical diagnosis. Although weight will clearly be given to abnormal investigations, such as a focal lesion on the MRI scan or evidence of generalised or focal EEG epileptiform discharges, none of these make the diagnosis of epilepsy. Epilepsy is a clinical diagnosis and any physician who enters court unable to substantiate the diagnosis on clinical grounds alone is likely to find themselves in trouble.¹

Role of the doctor as an expert

Criminal cases

A common question is whether an alleged crime has been committed when the accused has been having an epileptic seizure, or is confused following a seizure, and unaware of their actions (see above).

Less commonly, in an alleged murder, it may be argued by the defence that the deceased died as a result of a seizure, and not as a direct result of the assault. In such cases it is necessary to determine whether there was any prior history to suggest epilepsy and to consider the risk of death as a result.

Note that in criminal cases there is a higher burden of proof than in civil cases. The case must be established 'beyond reasonable doubt'. In civil cases, the case must be established 'on the balance of probabilities'.

The main factors to consider in such a case are given above (Section on Epilepsy and criminality) In brief:

- Is there an established, prior diagnosis of epilepsy?
- Is the alleged crime compatible with a seizure or automatism or post-ictal confusion, in terms of nature and complexity of actions, and duration?
- Is a claim of amnesia commensurate with that individual's seizures?
- The act should be out of character for the individual and inappropriate for the circumstances.
- Was there evidence of motive?
- Was there evidence of premeditation?
- Was there evidence of attempts to escape, or concealment after the event?
- Do investigations suggest a diagnosis of epilepsy?

Civil cases

Child protection. Cases are often brought by Social Services, or in matrimonial disputes, regarding child protection. The issue here is generally whether the epilepsy of one or both parents affects or prevents them from providing safe and effective child care.

If a child has developed epilepsy, it may be alleged that this is the result of non-accidental injury and that the parents are unable to care for the child.

Personal injury. If epilepsy develops, it may be questioned whether a prior insult, such as head injury, difficult birth, or medical accident, was the cause of the epilepsy, or whether this was coincidental. In such cases, the veracity of the diagnosis of epilepsy may be questioned and this may be difficult to resolve.

If liability has been admitted, the issues of the effect of the epilepsy on ability to live independently and to earn, and on life expectancy, will need consideration when determining the quantum of any settlement. The individual's life expectancy needs to be calculated according to the severity of the epilepsy and co-morbidities. It must be noted that life expectancy does not indicate how long the individual will live, but is a statistical estimate of average duration of life based on a population of individuals who are similarly affected.

Medical negligence

Most common claims by patients against doctors involve:

- Incorrect diagnosis, e.g. non-epileptic attacks diagnosed as epilepsy, with effect of loss of driving licence and livelihood; and failure to diagnose another treatable condition such as episodic cardiac asystole.
- Failure to diagnose and treat epilepsy, and possibly avoid subsequent serious complications or fatality.

- Failure to warn patients adequately about the effects and potential adverse effects of prescribed medical therapy or of surgical treatment. This includes the need to inform patients of the risks of discontinuing a medication and to have a 'fail safe' plan if the change of drug does not go well.
- The most common of these are: allergic reactions to medication, other chronic effects of medication (e.g. effects of retigabine on the skin and retina, vigabatrin on visual fields, effect of phenytoin on teeth and gums, effect of valproate on weight and menstrual cycle), interaction of antiepileptic drugs (AEDs) with other medication (e.g. oral contraceptive pill, warfarin), and teratogenic potential of AEDs, especially valproate.
- Failure to convey important information, e.g. the need to inform the DVLA of condition; safety issues, particularly drowning in a bath, burns from cooking; risk of death from seizures. This is a difficult area, as other professionals, such as GPs and nurses may also have a role in patient education and information.

Medical reports may be sought by firms of solicitors, from a patient's usual doctor, or from an independent expert witness, commissioned for the occasion. The conduct of Civil Cases was reorganised on 26 April 1999, following Lord Woolf's reforms of the Civil Justice System. The intention was that the legal process would become faster and more efficient. While this may be the case, a consequence is that expert reports are often requested by solicitors at an earlier stage, while considering whether to pursue a case.

Doctors as defendants

Most commonly this will involve allegations of medical negligence (VS). Also, breach of confidentiality.

The standard of medical care in a case of alleged medical negligence will almost invariably be judged by what is written in the medical notes. Thus it is even more important than ever to write clear, dated, legible and comprehensive medical notes.

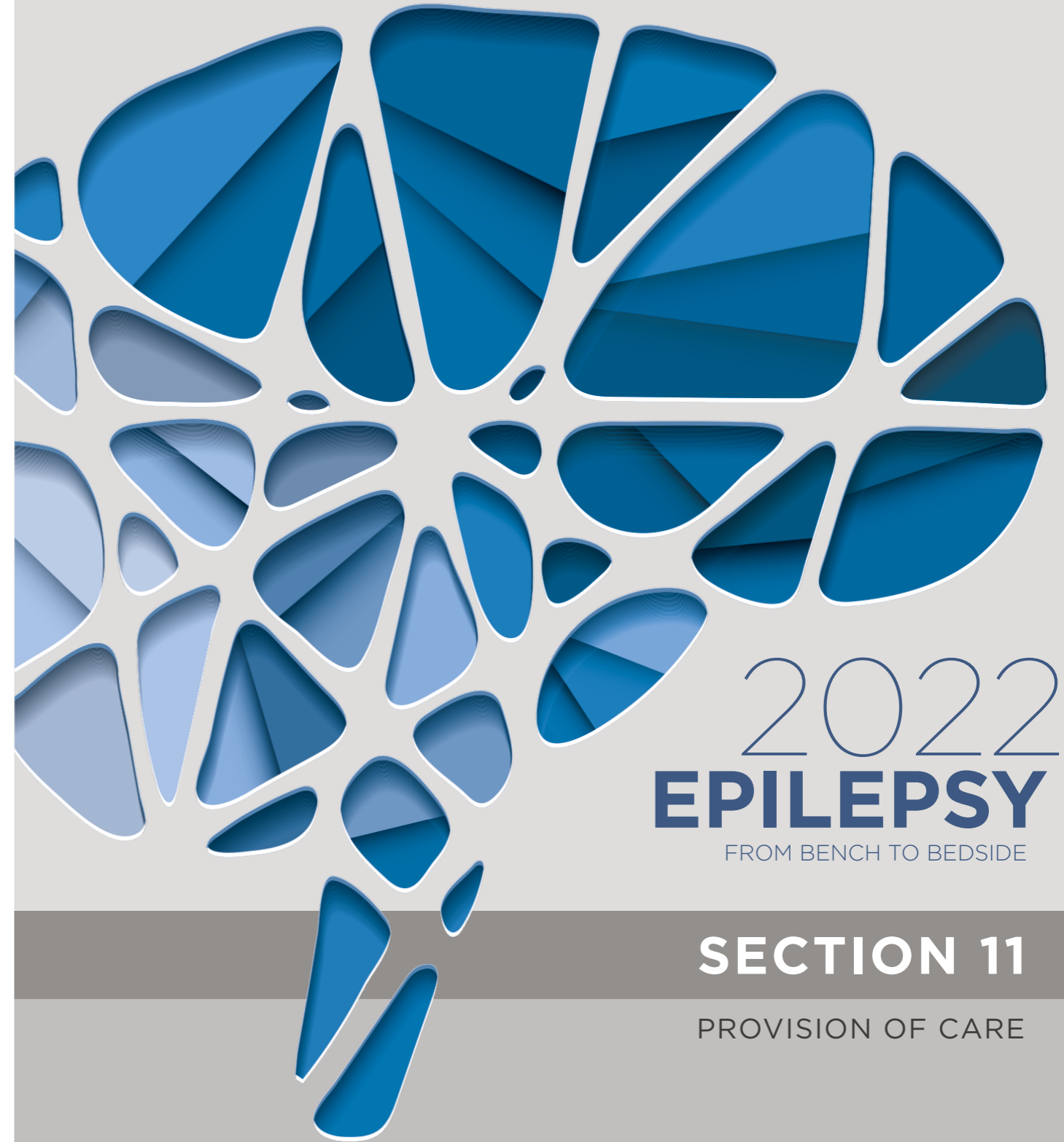
Lord Woolf's reforms set strict timetables for the conduct of cases. If these are not met, there is a risk of a case being found negligent by default. Warning signs are:

- A request from a patient for disclosure of records under the Access to Health Records Act 1990, in circumstances in which there is reason to believe that a patient may not have been satisfied with their medical care.
- A standard form or letter from a solicitor instructed by a patient, seeking disclosure of medical records for the purposes of a claim with which you could possibly be involved.

In the event of the above circumstances, it would be prudent to discuss the matter with your medico-legal defence organisation and, if appropriate, the Risk Management Department of the relevant NHS Trust.

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2022
EPILEPSY
FROM BENCH TO BEDSIDE

SECTION 11

PROVISION OF CARE

CHAPTER 57

Provision of clinical services for people with epilepsy

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Epilepsy is the most common serious neurological condition in the UK yet provision of care for people with epilepsy is patchy. The Clinical Standards Advisory Group (CSAG) report, published in 2000¹, noted 'a lack of focus for services for people with epilepsy and lack of co-ordination between primary care, secondary care, specialist centres and the voluntary sector'.

In 1997 the Scottish Intercollegiate Guidelines Network (SIGN) produced guidelines for the management of epilepsy², which were last updated in 2018³. The National Sentinel Clinical Audit of epilepsy-related death was published in 2002, and reported that a majority of people had received inadequate secondary care and estimated that 39% of adults' and 59% of children's epilepsy-related deaths were potentially or probably avoidable⁴. In response to this, the Department of Health published its Action Plan⁵ which focused the attention of health departments on epilepsy. Since the Action Plan, numerous government initiatives and reports have included epilepsy in their recommendations - most notably the NICE guidelines on the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Key points of the NICE guidelines were later summarised in the 2013 Quality Standards in Epilepsy (QS26)⁶, which provide a blueprint for epilepsy care in the UK. Epilepsy was the first neurological condition to be given quality standards (Table 1).

Table 1. Quality standard statements.

1.	Adults presenting with a suspected seizure are seen by a specialist in the diagnosis and management of the epilepsies within two weeks of presentation.
2.	Adults having initial investigations for epilepsy undergo the tests within four weeks of them being requested.
3.	Adults who meet the criteria for neuroimaging for epilepsy have magnetic resonance imaging.
4.	Adults with epilepsy have an agreed and comprehensive written epilepsy care plan.
5.	Adults with epilepsy are seen by an epilepsy specialist nurse who they can contact between scheduled reviews.
6.	Adults with a history of prolonged or repeated seizures have an agreed written emergency care plan.
7.	Adults who meet the criteria for referral to a tertiary care specialist are seen within four weeks of referral.
8.	Adults with epilepsy who have medical or lifestyle issues that need review are referred to specialist epilepsy services.
9.	Young people with epilepsy have an agreed transition period during which their continuing epilepsy care is reviewed jointly by paediatric and adult services.

In their report 'Epilepsy in England: time for change' (2009), Epilepsy Action highlighted the wide variation in provision of epilepsy services, with many Trusts and PCTs failing to meet the recommendations made by NICE⁷. Problems included:

- Inadequate access to specialists in epilepsy. Over half of all Acute Trusts and 64% of PCTs did not employ an epilepsy specialist nurse; and almost half of Acute Trusts surveyed did not employ an epilepsy specialist.
- Excessive waiting times for a first appointment (over 90% of Acute Trusts did not meet two-week waiting times).
- Inadequate access to diagnostic tests
- Lack of care plans and transitional services.

More recently in 2012 and 2014, two UK-wide epilepsy audits of hospitals with an emergency department (ED) provided site-specific quality standards benchmarked against all participating UK sites⁸. Although a small shift towards better care was seen between the first and second National audit, on each occasion a wide variation in quality was observed and much epilepsy care remained sub-optimal. Over half of individuals presenting to the ED were on monotherapy with one of the older antiepileptic drugs (AEDs) and were not under specialist review; and less than half the patients were referred onwards for specialist neurology input. What is evident is that there continues to be significant geographic and socioeconomic inequity in access to epilepsy care. Inadequate epilepsy care has significant financial ramifications as a result of unnecessary hospital admissions, epilepsy misdiagnosis, inappropriate use of emergency department resources and paramedic call-outs, and poor AED prescribing^{8,9}.

The National Service Framework, which sets out a programme for ten years to improve care of people with long-term conditions, mentions epilepsy¹⁰. Other publications, including the Expert Patients Programme¹¹, and the White Paper 'Our health, our care, our say'¹² encourage the participation of patients in their care. The chronic disease management (CDM) model was set up as part of an international drive to improve the quality of long-term care while containing health care costs¹³ (Table 2). Components of this model are highly applicable to epilepsy care.

Table 2. Summary of recommendations in the CDM model¹³.

Self-management	Integrated care	Clinical guidelines	Clinical information systems
Knowledgeable patient	Improve continuity and coordination of care	Evidence-based treatment and care	Timely sharing and exchange of clinical information
Active patient participation in partnership with healthcare practitioners	Multi-professional collaboration	Enhance quality and safety	Web-based electronic patient records
Improve compliance and adopt healthier lifestyles	Primary and specialist care partnership	Improve consistency of care	Health service monitoring, evaluation and planning
	Role expansion, e.g. nurse specialists	More efficient use of healthcare resources	

Primary care

The General Medical Services (GMS) contract was introduced in 2004 and is the contract between general practices and NHS England for delivering primary care services to local communities. Around the same time the government introduced the Quality and Outcomes Framework (QOF) which rewards GPs for the provision of quality care and helps to standardise improvements in the delivery of primary medical services throughout England. Participation in QOF is voluntary. The framework includes quality markers, and associated financial incentives, for the management of conditions, including epilepsy. For epilepsy, GPs can accumulate points for which they receive payment by demonstrating that they maintain a register of adults receiving drug treatment for epilepsy (read code EPO01).

Until 2014, practices also received funding for recording those aged 18 and over who were seizure free (EPO02) and the number of women of childbearing age who had received information and counselling about reproductive issues (EPO03) in the previous 15 months¹⁴. These last two quality indicators have now been retired¹⁵. Intuitively it would seem that improved-record keeping would translate into improved quality of care, and thence into improved quality of life for people with epilepsy; there are no randomised controlled trials available to support or refute this notion. The way in which the review was performed is likely to have impacted on the effectiveness of the process. If the activity was seen merely as a 'tick-box' exercise, then little would change for the better for people with epilepsy. If, however, GPs undertook proper reviews and instituted action plans, this may have improved the lives of people with epilepsy.

GPs often perceive their knowledge of epilepsy as inadequate and barriers to implementation of effective epilepsy review in primary care include: lack of incentivisation; the small numbers of people with epilepsy attending GPs leads to a perception of deficient knowledge and expertise; and poor access to secondary services. The Department of Health Action Plan suggested a specific framework to help develop more GPs and nurses with a special interest in neurology¹⁶. There have been GPs with a special interest in epilepsy for some time in parts of the UK¹⁷. There is, however, no accredited qualification for GPs with a special interest in epilepsy.

New diagnosis

The diagnosis of epilepsy is largely based on the history of seizures³, and the GP may well be the best person to take a detailed history from the patient and any eye-witnesses before salient features are forgotten. A GP with an average sized list can expect to see one or two people with new-onset epilepsy each year¹⁸. Because of the potential problems of diagnosis, it is recommended that a consultant neurologist, or other specialist with an interest in epilepsy, should see people with a possible diagnosis of epilepsy promptly. The 2015 SIGN and 2012 NICE guidelines both suggest that the diagnosis should be made by an epilepsy specialist, and that patients should be seen within two weeks^{3,19}. The SIGN guidelines also suggest that the 'shared care management system' should 'provide appropriate information' once a provisional diagnosis has been made, and the individual referred to a specialist centre³. The individual should be fully informed of the specialist's findings, as should the GP¹⁸.

The Epilepsy Needs Revisited document²⁰ suggested that GPs should not usually initiate treatment. This is reinforced by national guidance stating that the decision to start AEDs should be made by the individual and the epilepsy specialist. The NICE guidelines suggest that an epilepsy specialist should recommend the appropriate treatment, and also plan its continuation in partnership with the individual. Once the diagnosis has been established, the primary care team can help the individual to understand the implications of epilepsy. The following checklist for the first review of the patient by the primary healthcare team, after the diagnosis of epilepsy has been made, may be helpful¹⁸:

- Discuss the diagnosis
- Review seizure frequency; consider the use of a seizure diary
- Discuss drugs – the benefits and side effects
- Discuss the impact on the patient's lifestyle
- Find out what the patient knows and fill in the gaps
- Provide addresses of patient organisations
- Discuss contraception and pregnancy with women
- Agree a timetable for follow-up.

Active epilepsy

About 30% of people who develop epilepsy will continue to have seizures despite treatment with AEDs, and the Epilepsy Needs Revisited document suggested that most of these will require further specialist follow-up²⁰. In the absence of an accessible epilepsy nurse specialist, it is to the GP, however, that many people will have ready access when problems arise. CSAG¹ recommended that, for people in whom seizure control is sub-optimal, a management plan should be formulated jointly by the hospital and general practice. This would help to alleviate the mismatch which could occur when the person's epilepsy is being looked after by secondary or tertiary care, but when the individual has access only to the GP when acute problems occur. During routine visits, GPs should monitor drug dosages, seizure frequency, adverse drug effects, adherence to AED regimen and any other problems¹. The NICE guidelines further propose that, for each person with epilepsy, there should be a comprehensive care plan, agreed between the individual and primary and secondary care providers, and which includes medical and lifestyle issues¹⁹. People should receive appropriate information and education about all aspects of epilepsy, and some can be encouraged to manage their epilepsy more effectively through the Expert Patients Programme¹¹.

Controlled epilepsy

It is generally accepted that those no longer experiencing seizures can be returned to primary care with provision for re-referral when necessary. The NICE guidelines suggest that people should have a regular structured review, performed by either the GP or specialist depending on the circumstances and severity of epilepsy, which should occur at least once a year¹⁹. Many practices in primary care have built in templates for annual epilepsy reviews with read codes and standardised templates have been incorporated into electronic patient records to facilitate teaching and to guide the review process.

The GP should re-refer the person to secondary care if the seizures are inadequately controlled, or if there are specific medical or lifestyle issues, such as pregnancy or consideration of withdrawal of AEDs.

Those not under current review

There may be problems in attempting to review all people with epilepsy, particularly those who have not been reviewed for some years. People may not wish to be reminded of the diagnosis, which may have been denied or concealed²¹, and there may be anxiety about the prospect of change²². The best time to offer a review may be when a prescription is due²¹. In keeping with the goal of person-centred medicine, it is suggested that the first requirement is to define the main problems as seen by the person; whether directly seizure related, AED side effects or psychosocial problems²¹. The correctness of the diagnosis should be challenged, the frequency and severity of seizures ascertained, and all aspects of AED therapy, including adherence to drug regimen, discussed.

It has been shown that reviewing people with epilepsy in general practice, reducing polytherapy and changing treatment, can improve seizure control in over one-quarter of patients, and reduce side effects in almost one-quarter²¹. In many cases, however, re-referral to specialist care for these alterations may be more appropriate.

Integrated epilepsy care and community epilepsy schemes

Epilepsy care has traditionally been fragmented, with poor channels of communication between primary and secondary care¹, and between epilepsy specialists and the wider multidisciplinary team. People with chronic epilepsy often have significant comorbidity requiring psychological support and the input of mental health and social care services. Uncoordinated care can lead to inconsistent advice for patients, inappropriate and unnecessary investigations and interventions, and delays in diagnosis and initiation of treatment²³. Improved integration of care is key to improving the quality, safety and efficiency of health services for people with chronic disease.

This whole systems approach encouraging collaboration between different health sectors underlies the Sustainability and Transformation Plans (STPs), which will become the main sources of funding and service development from 2017/18 in England. STPs are five-year strategic plans detailing how organisations will work together to create plans based on local health needs in 44 different geographical 'footprints'. In a change of direction, STPs will be centred around the needs of local areas and their populations, rather than the activities of individual organisations.

For some time, community epilepsy nurse specialists, community learning disability nurses and GPs with special interest in epilepsy have helped bridge the gap between primary and secondary care, providing a comprehensive epilepsy service in the community following initial diagnostic evaluation in secondary care. A survey of patients' perspectives on services for epilepsy reported that 'most people with epilepsy (67.6%) would prefer their care to be community based, especially older patients and those with mild epilepsy²⁴. Epilepsy nurse specialists are integral to effective integrated care, evaluating need and access to multi-agency community services, providing information and support to patients, their families and carers, and improving patient knowledge and self-management. To date, the impact of nurse intervention on health outcomes such as impact on unplanned admissions, seizure outcome and cost is largely unexplored, but it is widely acknowledged that epilepsy specialist nurses enhance the integration of epilepsy care and improve patient experience.

There has been a recent move by some clinical commissioning groups (CCGs) to commission and develop more integrated community-based epilepsy services. One such model (pilot study, Camden CCG) aimed to provide a 'Step up and step down service' as an interface between primary and secondary care. Individuals were seen by epilepsy specialists in the community, allowing improved communication with GPs and better implementation of epilepsy care plans. People with stable epilepsy and those with complex care needs were stepped down into the community service, allowing greater access to allied health professionals and improved communication across services. It is anticipated that delivering care in the context of integrated health and social care provision with regular MDT meetings will better address the wider burden of epilepsy (such as social exclusion, anxiety and depression), while offering improved psychosocial support, and better access to employment advice and local support networks.

Integral to effective integrated care is timely sharing and dissemination of clinical information. A unified electronic care record system is required to enhance coordinated patient care and allow data to be captured and interrogated. Improved integration across primary, secondary and tertiary care and social services should result in improved sharing of information and ultimately improved patient experience

Specialist care

After diagnosis, 20-40% of people with epilepsy will need follow-up in a specialist centre²⁵. The CSAG report recommended that epilepsy care should be based on epilepsy centres. These

would be well organised with good links to other services and with emphasis on shared care and communication between the centre and general practices¹.

The NICE guidelines do not specifically address models of care, or recommend what form of service configuration can best provide the resources required. A Cochrane Review found only one study investigating the benefit of clinics held at a specialist epilepsy unit²⁶. The study had a weak design and the review concluded that there was no robust evidence for benefit of the specialist clinic. Nevertheless, several studies have shown that neurology opinions may contribute useful advice to, or change the diagnosis in, patients previously under the care of non-neurologists^{27,28}, and the Association of British Neurologists states that neurologists who specialise in epilepsy (or other conditions) are better at managing those conditions than neurologists without such a specialism²⁹. Whatever form the clinics take, there is agreement that people needing specialist care for epilepsy should be treated by a specialist with an interest in epilepsy. A study from the north of England suggested that older people with epilepsy are less likely than younger people to be referred to specialist epilepsy services³⁰.

The transition and transfer of epilepsy care for adolescents is specifically endorsed by NICE¹⁹, SIGN³ and the NSF¹⁰. Transition from paediatric to adolescent services is a major milestone for an adolescent with a chronic illness such as epilepsy, with adjustments in their care and social needs as well as an evolving relationship with their parents and clinicians. Although 'transfer' and 'transition' are often used interchangeably, transition is a more dynamic process implying a planned and structured move from paediatric to adult care, involving preparation and discussion with the young person, while transfer often represents a single event of passing their medical care either back to their GP or to an adult or specific adolescent service.

Specialist epilepsy care should provide provision for special groups, e.g. adolescents, patients with learning disability and women with epilepsy requiring preconception advice. Such services could conceivably be held either in the community or in specialist units and funding may come from either hospital Trusts or Clinical Commissioning Groups.

New diagnosis

The function of the hospital service in people who develop seizures is to:

- Confirm the diagnosis
- Initiate treatment, if indicated
- Provide initial counselling and information to patients and their families
- Monitor the response to the initial treatment, and
- Refer the patient back to the GP if the condition is stable²⁰.

The NICE guidelines¹⁹ propose that the diagnosis of epilepsy should be established by specialist practitioners with training and expertise in epilepsy. (Misdiagnosis of epilepsy is common, occurring in up to one-quarter of patients referred to a specialist clinic³¹ and in at least one-fifth of people from primary care who were assessed by a specialist³²; there may be physical, psychosocial and socioeconomic consequences of a misdiagnosis.) After a detailed history of the attack has been obtained from the patient and any eyewitnesses, a full physical examination, including cardiac, neurological and mental state, should be carried out. Appropriate investigations should be available where necessary. The guidelines stress that information on how to recognise a seizure and first-aid for seizures should be provided to the individual, to the family and to carers. Some information should be provided while the diagnosis is awaited. Once epilepsy is diagnosed, seizures and syndromes should be classified using a multi-axial diagnostic scheme. The decision to start AED treatment should be made after full discussion of the risks and benefits, taking account of the person's epilepsy syndrome, prognosis and lifestyle. Treatment (where appropriate) should

be initiated by the specialist, who should also plan the continuation of treatment and manage, or provide guidance for, withdrawal of AEDs.

Active epilepsy

Those with continuing seizures should benefit from continuing secondary care, with additional investigations and treatments being available. Video telemetry and high resolution MRI may be indicated, and the patient may need to try second-line or experimental drugs, or be assessed for epilepsy surgery or neurostimulation²⁰. All people with epilepsy should be able to consult a tertiary care specialist (via the secondary care specialist) should the circumstances require this¹⁹. Suggested criteria for referral to tertiary care are:

- Epilepsy not controlled with medication within two years, or after two AEDs
- Unacceptable side effects of AEDs
- Presence of a unilateral structural lesion
- Psychological or psychiatric comorbidity
- Diagnostic doubt¹⁹.

Controlled epilepsy

Although those adults who become seizure free will probably not need ongoing secondary care, it is important that re-referral can be swiftly instigated should seizures recur, or circumstances change (e.g. impending pregnancy). NICE suggests that AED withdrawal should be discussed with adults who have been seizure free for at least two years; it is important that this decision is made by the patient and the specialist after a full discussion of the risks and benefits, and that the withdrawal be under the guidance of the specialist¹⁹. In children a regular structured review, occurring at least yearly, should be provided by a specialist¹⁹.

Accident and emergency care

In line with the findings of the NASH reports, a survey in Leeds in 1998 showed that fewer than one-quarter of people with epilepsy-related emergencies seen in A&E were referred for neurological follow-up, noted to be under regular specialist follow-up or admitted to the neurology ward³³. A more recent audit of 38 persons with a first seizure seen in an A&E department found that, of 22 people discharged, either with an appointment to see a neurologist or a letter to the GP advising such referral, only 10 (45%) were seen by a neurologist³⁴. The mean wait was 21 weeks (range 6–44 weeks).

The NICE guidelines recommend that A&E departments should develop first seizure protocols to ensure that people with suspected seizures are properly assessed and that, once initial screening has been performed by a suitable physician, urgent referrals to a specialist are made¹⁹.

Patient education and self-management

Most epilepsy publications stress the importance of information provision for people with epilepsy^{1,18,20,35,36}. Empowering individuals to take a more active role in their care is likely to improve their understanding of their condition, develop greater awareness and management of their triggers, encourage adoption of healthier and safer lifestyles and use scarce health services more efficiently. Improved partnership between the individual and clinician in devising a care plan should help to increase treatment adherence. It has been reported that inadequate adherence to AED regimens occurs in 30–60% of patients³⁷. Self-management programmes, e.g. MOSES (Modular Service Package Epilepsy) and SMILE (Self-management in epilepsy) have been shown to improve: knowledge of epilepsy, coping with epilepsy, peer support, seizure frequency and tolerability of AEDs^{38,39}.

The last few years have also seen the rise of mobile technology in educating and supporting self-management skills, potentially accessing larger patient populations. An innovative self-monitoring mobile app, EpSMON, educates and empowers service users to monitor and address their own risks based on a SUDEP risk safety checklist⁴⁰.

Conclusion

In response to ever increasing burdens on our healthcare system and the wide variability in the quality of epilepsy care across the UK, there has to be a change in the way epilepsy and other long-term conditions are managed. Management needs to move away from the episodic reactive model of epilepsy care to a more proactive model that averts or delays unplanned admissions, promotes patient participation through improved self-management and improves the quality of life of those with epilepsy. Although much progress has been made in developing quality standards in epilepsy, in reality, guidelines are often poorly supported and implemented. Transforming epilepsy care requires individual and importantly organisational change in developing new models of integrated care that cross organisational boundaries and provide more pro-active patient-centric care.

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CHAPTER 58

The role of the voluntary organisations in epilepsy

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Charities in the UK pre-date the Victorian period significantly. But it was in the 19th century that charity as a culture really took root in response to the poverty, deprivation, lack of hygiene and poor health of a society that had no welfare state.

Charities as we know them today were founded as a response to inequality. But in the more enlightened 21st century, with a digital NHS, sophisticated welfare system and an environment of inclusivity, equity and education for all, do charities or voluntary organisations still have a role to play?

You barely need to scratch beneath the surface to find the answer. The disparity in health and quality of living according to wealth remains alarming. And the rate of deaths associated with epilepsy in areas ranked as the most deprived in England is nearly three-times greater than in the least deprived areas: 13 deaths per 100,000 population against 5 deaths per 100,000 population.

Data collected from the Office of National Statistics between 2009-2013 shows rates of premature death vary vastly within England, creating a postcode lottery: someone with epilepsy is 49 per cent more likely to die prematurely in West Yorkshire than in Cheshire.

If the statistics are clinical, the stories are compelling. Helplines are the mainstay of many charities. Four of the UK's largest epilepsy charities - Epilepsy Society, Young Epilepsy, Epilepsy Action and SUDEP Action - all have their own helplines, which provide a listening ear and often a lifeline for people affected by epilepsy. But they also provide a barometer for an unmet need in a society and system that cares but often fails to deliver.

Calls around sodium valproate and medicinal cannabis come in waves and can be driven by media activity. Epilepsy Society's helpline takes increased calls around these issues whenever high-profile stories hit the headlines. But there are some issues which are a constant. Issues around disability benefits. Issues around medication shortages. Issues around loneliness and lack of access to services which could make a difference to quality of life.

Despite reforms to social care, people with epilepsy - a poorly understood fluctuating condition - still must fight for the right to benefits which would be a given in another condition.

Despite a prescription for often multiple medications, finely tuned over many months if not years, people with epilepsy face shortages of medications on a regular basis with the untold stress and anxiety that this creates, risking the trigger of a seizure.

There are 600,000 people living with epilepsy in the UK. For one third of those people, their seizures may not be controlled by current treatment options. For every person with epilepsy, controlled

or uncontrolled, there will be a network of friends, family, teachers, employers, colleagues, neighbours, members of the public, who are also impacted by that person's epilepsy. The condition may only affect one person in a hundred, but the extent of that impact reaches far wider.

Do voluntary organisations and charities still have a role to play in the 21st century? The answer would be an unequivocal 'yes' and probably more so today than in any other era. Charities are there to hold politicians, Government, regulators and the healthcare system to account.

Charities and voluntary organisations are no longer patriarchal, remote advocates for the people they represent. They are member-led organisations that empower and work with their supporters to bring about change. The voice of the patient is far more powerful than the voice of the charity in telling a story. And with social media firmly embedded in our social structures, the voice of the people is louder today than ever before.

Online communication tools - Facebook, Twitter, Instagram, email - have taken campaigns off the street and straight into the inboxes, personal 'streams' of those who can make a difference. Charities remain key in influencing and advocating for people with epilepsy, and the people themselves are the voices that make politicians sit up and listen.

Recent campaigns by Epilepsy Society have engaged with politicians at Government level to tackle issues that affect people with epilepsy: medicines shortages and the safeguarding of people with photosensitive epilepsy online. The charity has called for the Health Secretary to commission a review of the medicines supply chain and has asked the Government to safeguard people with photosensitive epilepsy through its Online Harms White Paper.

Young Epilepsy has launched an online guide for schools to tackle the lack of epilepsy awareness in the education system; Epilepsy Action has been campaigning to improve access to Personal Independence Payments for people with epilepsy; SUDEP Action has been campaigning around epilepsy patient safety.

Charities are also a funnel for philanthropic giving, enabling Trusts, Foundations and affluent givers to be an important part of translating today's research into treatments for tomorrow's patients, through funding pioneering research projects.

But online communities are pushing forward the boundaries of research too, through charities. Families and friends with loved ones affected by a condition such as epilepsy are the greatest champions for change in the field of medicine and have the greatest investment in the need for better diagnosis and treatment options.

Every day supporters run, cycle, jump, sky dive, bake or undergo head shaves to raise money to help fund research into the underlying causes and treatments of epilepsy.

Charities are about team work at every level. They are about working with people and with politicians to bring about change. They are about holding regulators and the healthcare system to account. They are about listening and responding.

For a small number of people with complex epilepsy and associated disabilities, Charities are also about providing bespoke 24-hour care to enable them to live as full a life as possible.

When Epilepsy Society was founded in 1892, it was about providing an alternative lifestyle for people with epilepsy who would otherwise end up in the work house or gaols. Today it is about supporting people to achieve their goals in a community that is as accepting of epilepsy as it is of other conditions such as asthma. And it is about unravelling the genetic architecture of epilepsy so that we can improve diagnosis and treatment of the condition, improving outcomes for everyone with a diagnosis of epilepsy.

CHAPTER 59

The Role of the Epilepsy Nurse Specialist: Past, Present and Future

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The Past

The role of the nurse has evolved significantly since the time of Florence Nightingale. Diploma, degree and master's education has expanded the scope of nursing practice. The term clinical nurse specialist was coined in the 1940s¹. In part as a reaction to the significant loss of doctors during the war years there was a need to bridge the expertise gap with the nursing workforce. The role of Clinical Nurse Specialist (CNS) and Advanced Nurse Practitioner (ANP) started to gain pace from the 1980s onwards and the establishment of Nurse Consultant posts has enabled further enhanced patient care.

In 1988, the first UK epilepsy clinical nurse specialist post was developed by a community service in Doncaster, England. By the 1990s the number of epilepsy nurse specialists had reached double figures and a professional body called ESNA (Epilepsy Nurses Association) was established in 1992². In 2004 ESNA had 120 members and 170 associate members, with the organisation holding yearly conferences, regular local group meetings and publishing a professional journal³. Further posts were created when Glaxo Wellcome helped fund Sapphire Nurse Posts by joining forces with Epilepsy Action to celebrate the 45th anniversary of the founding of the charity. By 2007 Epilepsy Action had provided funding for 83 Sapphire Nurse posts, investing £2.5 million into the UK health service⁴. In 2017, ESNA developed competencies for practice providing an excellent framework for practice development from novice to expert⁵.

The Present

There are currently over 350 ESNA members but not all epilepsy CNS's, ANP's or Nurse Consultants are registered with the organisation². The vast majority of epilepsy CNS's will have first level degrees, whilst Nurse Practitioners and Nurse Consultants have, or are working towards, Masters level in Epileptology, Neurosciences or Advanced Nursing Practice, and may consider doctorate qualifications. A large number are independent prescribers. Knowledge, expertise and experience varies widely⁴. For this chapter, all of the above-mentioned roles will be described under the umbrella of 'Clinical Nurse Specialist' (CNS) or 'Epilepsy Nurse'.

The background of paediatric and adult epilepsy nurses is diverse. Often there is experience in neurology, neurosurgery or learning disability but beyond that there is a rich and a wide variety of experience amongst the epilepsy nursing force. Epilepsy CNS work in a wide variety of settings across healthcare ranging from acute trusts through to community services. Clinical support and supervision again vary⁴. Some post holders work in isolation with visiting neurologists covering large geographic community areas, others as part of an epilepsy nursing team in large neurosciences centres working with a large multidisciplinary team (MDT)⁴. A report by Epilepsy Action found an average caseload of 570 patients. Some had caseloads of up to 2,400⁶.

Definition

The definition of a Clinical Nurse Specialist states nurses “serve as experts in evidence-based nursing practice integrating their advanced knowledge of disease processes in assessing, diagnosing, and treating people with epilepsy, but their role extends beyond providing patient care”⁷ Chang and colleagues identified 5 key roles for the nurse specialist⁷ (figure 1).

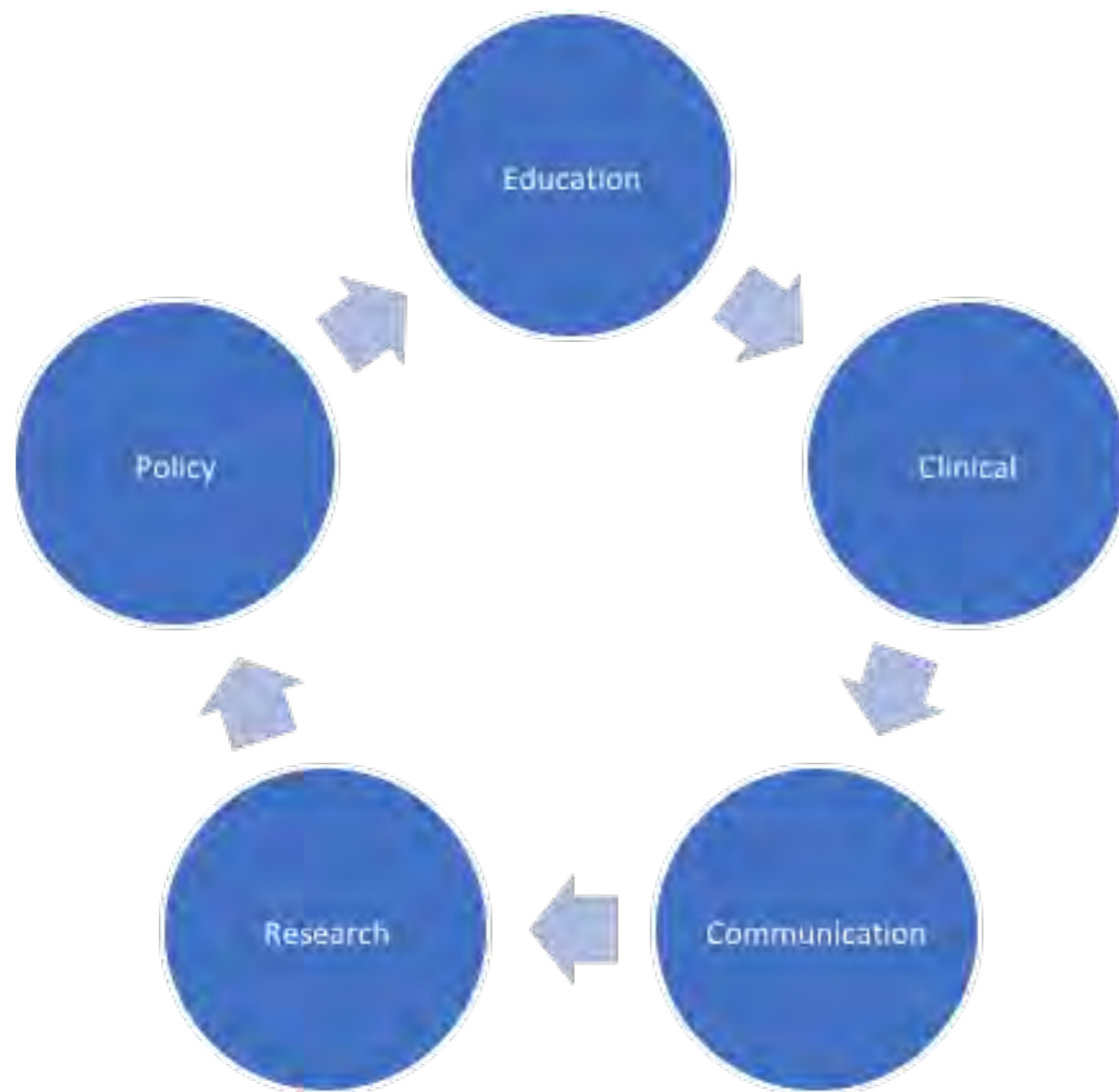


Figure 1.

Education

Expert provision of education underpins the role of the epilepsy nurse. Patient education is provided at the hospital bedside, during home visits, in an out-patients clinic, in a group education setting and via telephone and email. Due to the nature of the condition, seizures will

impact on all aspects of a person’s wellbeing. National Institute for Healthcare Excellence (NICE) describes no less than 20 topics to discuss with new epilepsy patients which can be overwhelming to cover and is not realistic in a single consultation⁸. 40-80% of medical information patients receive in a consultation is forgotten immediately and the more information provided, the lower the proportion correctly recalled⁹. Epilepsy nurses can disseminate health information in longer consultations and can see patients more frequently, increasing the opportunity for patients to retain essential health information. The epilepsy nurse can spend time going through complex topics such as pre-conception counselling, epilepsy surgery or provide brief-but-essential follow-up calls when patients are changing medications. Re-visiting topics such as contraception, lifestyle and safety should not be underestimated. Any patient with a new diagnosis ideally should attend with an advocate such as a parent/partner, other relative or friend. Family/advocates often provide valuable witness accounts and clinical history but also improve the retention of information and reinforcement of advice post-consultation. This is particularly important for young or vulnerable patient groups.

NICE summarises the topics that are recommended for any new patient:⁸

- epilepsy in general
- diagnosis and treatment options
- medication and side effects
- seizure type(s), triggers and seizure control
- management and self-care
- risk management
- first aid, safety and injury prevention at home and at school or work
- psychological issues
- social security benefits and social services
- insurance issues
- education and healthcare at school
- employment and independent living for adults
- importance of disclosing epilepsy at work, if relevant (if further information or clarification is needed, voluntary organisations should be contacted)
- road safety and driving
- prognosis
- sudden death in epilepsy (SUDEP)
- status epilepticus
- lifestyle, leisure and social issues (including recreational drugs, alcohol, sexual activity and sleep deprivation)
- family planning and pregnancy
- voluntary organisations, such as support groups and charitable organisations, and how to contact them.

A seizure is often frightening to experience and to witness. Detailed explanation of what happens during a seizure and how to manage them can make a huge difference to the person’s ability to adjust to a diagnosis. A survey by Sue Ryder foundation in 2016 found that people were more frightened about a diagnosis of a neurological condition like epilepsy than a diagnosis of cancer¹⁰. There is tremendous fear and stigma attached to a new diagnosis of epilepsy¹¹. Education is essential to minimise the psychological impact. The 2012 UK National Audit of Seizure Management in Hospitals found that people with epilepsy received poor provision of information¹². Clearly there remains a need for a more robust system to provide patients with the right information at the right time. Epilepsy nurses are well placed to address this gap. Nurses play a key role in developing epilepsy knowledge in their healthcare organisation, for example training for pre and post registered nursing and for allied health professionals. In the community setting epilepsy nurses support GP’s, develop self-management education and are a point of contact for people or organisations requiring further epilepsy knowledge.

Clinical services

Essentially, the aim of the epilepsy nurse is to provide a seamless care pathway from initial first suspected seizures through to ongoing management of those with drug resistant seizures. The NHS

was founded on the concept of health care from cradle to grave. The epilepsy nurse is perfectly placed to support infants/children and their families with smooth transition to adult services right through to supporting the older person developing seizures.

It is important to highlight that although paediatric and adult services will have many similarities there will also be differences. The RCN in collaboration with ESNA has developed competencies for paediatric epilepsy nurses¹³. Despite the development of competencies and job specifications across the UK in both adult and paediatric epilepsy nursing, the day-to-day activities of epilepsy nurse roles remains diverse^{4,5}. Each service will be tailored to local needs. Below are examples of the types of clinical services epilepsy nurses can provide:

Nurse-led clinics are now common practice in the outpatient setting. Although some areas continue to provide joint consultations with consultant and nurse, the use of a nurse-led service can improve efficiency¹⁴. Nurse-led clinics are defined by Foley as “an independent organised setting providing on-site and offsite services with the administration, supervision and co-ordination of care by registered nurses and with formal protocols that ensure the arrangement of consultation or referral as needed. It brings total healthcare skills, including therapeutic listening, supportive counselling and motivation, and a long-term case management perspective”¹⁴. Attending a nurse-led clinic can improve compliance and provides high-quality, cost-effective care¹⁵. In clinics, nurses provide expert assessment skills including history taking, risk assessment, antiepileptic drug knowledge and interpretation of test results. Medication management is seen as a large part of the role in the clinic setting⁶. The epilepsy nurse will assist titration of often complex drug regimes in those with drug resistant epilepsy. Adherence to treatment can be improved with education and regular review. Although the reasons behind poor adherence to treatment remain complex, the relationship between health professional and patient has been identified as a key factor¹⁶. The epilepsy nurse can provide this crucial relationship and continuity of care.

First seizure. All patients should have a review with a consultant neurologist following a suspected first seizure⁸. These frightening events require timely provision of support and education around driving, employment and safety. Early intervention and access to a witness account will support accurate diagnosis and management minimising misdiagnosis¹⁷. The Epilepsy Nurse can provide a review in A&E, alongside the first seizure consultant clinic or provide triage clinics both face to face or via telephone clinics¹⁸.

Transition. The government guidance suggests transition should start from age 14 years^{19,20}. Southampton University has developed an excellent transition tool, Ready Steady Go. Documentation can be obtained from ReadySteadyGo@uhs.nhs.uk. Both paediatric and adult nurses can work together with the wider neurology team to support young people to transition smoothly to adult services. Both nurse and joint consultant clinics support young people with epilepsy, for example by navigating independent use of medications, education and employment barriers, recreational activities such as alcohol and drug use, driving and the impact on mental health and relationships.

Learning Disability (LD). Another group of vulnerable patients more prevalent in the epilepsy community are those with intellectual disabilities. These patients often have the most difficult-to-control seizures and may require detailed care planning, for example protocols and education for rescue medication. These patients often have a risk of multiple A&E admissions to hospital and their families need significant support. The epilepsy nurse can co-ordinate care with local LD services. Patients, carers and families need a high level of support where there are often complex social and physical needs²¹. The epilepsy nurse can provide specialist clinics, these may be joint clinics with a learning disability nurse or MDT clinic setting involving professionals such as LD consultants and neurologists.

Women’s Services. Seizures and epilepsy can be impacted by hormonal changes⁸. Epilepsy nurses support women from transition as a teenager choosing contraception, planning and monitoring a pregnancy, through to the effect of the menopause. Specialist women’s services may include a pre-conception clinic, epilepsy antenatal service to monitor high risk pregnancy, and collaborative work with antenatal medical and midwifery colleagues. Pre-conception counselling has had an increased profile in recent years following the Medicines and Healthcare products Regulatory Agency (MHRA) guidance on women taking valproate. (<https://www.gov.uk/guidance/valproate-use-by-women-and-girls>).

Older person. With an aging population there is increasing focus on managing chronic conditions²³. In the epilepsy population, we are seeing increasing cases in over-65s developing seizures. These patients may be difficult to diagnose and manage. Many people with epilepsy in this group have difficulty tolerating medication, polypharmacy, cognitive impairment and social isolation^{22,23}. The epilepsy nurse can work with community and older person teams to support patients and a dedicated clinic may be beneficial.

Oncology liaison. A seizure can be the presenting symptom identifying a cerebral lesion⁸. Those with low grade gliomas through to patients with aggressive cerebral tumours can develop seizures which can potentially be difficult to control. The epilepsy nurse will liaise with oncology colleagues and provide much needed support to patients who are managing an already difficult health crisis.

Epilepsy Surgery/VNS. 30% of patients are deemed drug resistant and may pursue surgical treatment options⁸. Invasive resective surgery, Vagus Nerve Stimulation (VNS) or Neuropace are possible options. Any patient considering epilepsy surgery requires extensive investigation for suitability. Epilepsy nurses can support patients through the process, thus enabling informed choices. Specialist clinics are often provided by epilepsy nurses in conjunction with the neurology and neurosurgical team, for example VNS monitoring.

Social management. The social impact of the condition requires an understanding of employment restrictions, housing requirements, driving regulations and the psychological impact. Morgan and colleagues identified that there is a correlation between prevalence of epilepsy and social deprivation²¹. This group of patients were also less likely to have seizure control in the previous year. Those with complex social challenges often require support with housing and benefits. The Epilepsy Nurse will usually address social needs as part of a holistic approach to care in every patient contact.

Communication – managing complex caseloads

Effective communication is one of the most essential skills in healthcare. NHS England in the document ‘Compassion in practice’ describes communication as “central to successful caring relationships and to effective team working. Listening is as important as what we say and do and essential for ‘no decision about me without me’”²⁴. Epilepsy Nurses play a pivotal role in case management – they are the point of contact working in collaboration with medical colleagues to provide timely and expert advice for both patients and professionals.

It is well known those with a diagnosis of epilepsy have increased risk of co-morbidities, both physical and psychological²⁵. Epilepsy patients are more likely than the normal population to develop depression and anxiety²⁶. The mortality rate is at least double the normal population with an increased risk of suicide²⁶. This results in often a very complex caseload requiring significant interventions. It is the expectation that an epilepsy nurse will be a skilled communicator with both patients and fellow professionals. It is the author’s opinion that communication is the bedrock of the post.

Research & Policy

Clinical audit and research are key elements of the role. National and international studies are strongly supported by the epilepsy nursing work force. It is the expectation that all epilepsy nurses will provide continuous audit of the role and participate in or lead research to improve the lives of people with epilepsy. It is the author's view that epilepsy nurses are often focused on clinical care and supporting patients, limiting their time available for research, despite its importance. In the current healthcare climate with restricted funds, participating in research can be an essential tool to support the development of epilepsy nurse roles.

Although the epilepsy nurse role is well established, in the past their value has been challenged¹⁸. A recent report from the RCN examined the contribution nurse specialists make towards high quality care. They found 'compelling evidence of the impact of specialist nurses' and it makes recommendations for investment in specialist nursing across all areas of practice. They summarise that nurse specialists:²⁷

- apply specialist and specific knowledge and skill to manage physical and psychological morbidity
- alleviate physical and psychological suffering inherent in this long-term condition
- use vigilance of physical symptoms and drug toxicity to trigger rescue work
- co-ordinate complex care and refer onto other professionals as part of the multi-disciplinary team (MDT), particularly the community services
- provide patients with a contactable, knowledgeable, and accessible professional
- provide clinical expertise to patients, families and other professionals, e.g. GPs
- resolve unsatisfactory experience represent good value for money, through reducing costs in primary care and saving consultants' time.

Epilepsy patients managed by epilepsy nurses have a high degree of satisfaction and are well informed about their condition^{14,25,28}. Risdale and colleagues tested the feasibility and effect of nurse-led Epilepsy Clinics in primary care. They found nurse-led clinics for patients with epilepsy are feasible, well attended and significantly improve the level of advice and medication management²⁹. The recently published ESNA competencies summarise the benefits of the role, stating "The Epilepsy Specialist Nurse is pivotal in providing a greater understanding of the condition and adopting a holistic, collaborative and co-ordinated approach that can help reduce the impact of epilepsy on the individual and their family"⁵.

Epilepsy nurses play a strategic role in service development shaping the way we care for patients who experience seizures. In the current financial climate there is increased pressure to ensure efficient streamlined services. A nurse specialist can be instrumental in providing a cost effective and efficient service for health care providers by:

- Reducing admissions - A&E
- Reducing hospital stays

- Providing education and support - limiting employment difficulties / support for schools, keeping people in education and the workforce
- Accessible services - GP support, reducing number of referrals to secondary / tertiary care management in the community

The National Clinical Audit of Epilepsy-related Death identified that there were deficiencies in the overall quality of epilepsy care in general practice and hospitals, on a range of issues. 54 per cent of adults and 77 per cent of children received inadequate care and 42 per cent of epilepsy deaths annually were potentially avoidable³⁰. With this in mind, there is an urgency to improve patient services. NICE has recommended that all patients should have access to an Epilepsy CNS⁸. Engaging all potential stake holders to support proposals is essential. The following documents are useful resources:

<https://www.nice.org.uk/guidance/qs27/resources/support-for-commissioners-using-the-quality-standards-for-the-epilepsies-in-adults-and-the-epilepsies-in-children-and-young-people-pdf-253621981>

NICE. *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care*. Clinical Guideline 137. Available at www.nice.org.uk/cg137

Epilepsy Tool kit- <http://www.epilepsytoolkit.org.uk>

Future

Despite huge leaps in technology, as yet Artificial Intelligence has not replaced the clinical team. Technology may change the way we communicate with our patients. The traditional outpatients' setting may become obsolete. How we manage patients across primary and secondary care is constantly evolving with a greater emphasis on management in the community setting. Therefore, the traditional primary, secondary and tertiary model of epilepsy care may change. Technology in the home such as home Video-Telemetry, alert systems, smart devices and improved communication methods such as video calls will no doubt change the landscape of health care. Services will need to adapt to these developments. Ultimately, care cannot be superseded by technology. It is the author's view that patients will always require specialist trained doctors and nurses to support them. Advances in technology cannot replace the fundamentals of nursing care. NHS England identified 6 core nursing values: Care, Compassion, Competence, Communication, Courage and Commitment²⁷. Although the CNS role can vary dependant on local needs all epilepsy nurses have the same goal - to improve the health and wellbeing of people affected by epilepsy and will aim to embed these values into the service they provide.

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