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 medicine[5].

'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 socially[5]. 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 status[7]. As such, they are contraindicated in IGE which make up one-third of 'epilepsy' cases[5] 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 seizure[8].

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 epilepsy[6]. Patients may often suffer many minor seizures long before or after their 'first seizure' or 'last seizure'[6].

Epileptic seizures are classified[10] 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 morbidity[2].

Syndrome/disease diagnosis

The diagnosis 'epilepsy' is no more precise than the term 'seizure' and similar arguments weigh against its use[6]. The World Health Organization Dictionary of Epilepsy[11] 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 Epilepsy[2] 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 imbalance[2].

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 diagnosis[2].

This classification[2] 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 epilepsy[12]. 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 syndromes[2].

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 JME[21].'

The syndromes of temporal lobe epilepsy

The syndromes of temporal lobe epilepsy comprise more than 30% of epilepsies. They are an 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 benefit[22].

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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