Chapter 27

Managing refractory epilepsy

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Refractory or drug resistant epilepsy develops in 20–30% of all patients diagnosed with epilepsy. The ILAE has suggested that a person be considered to have refractory epilepsy if they have failed to achieve sustained seizure freedom with two appropriate and tolerated antiepileptic drug (AED) regimens[1]. 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%, respectively[2]. 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 well[3]. Patients with refractory epilepsy are less likely to acquire qualifications, be employed or married, or live independently[4]. Management of this complex disorder requires appreciation not only of its physical manifestations, but also the psychological, psychiatric and societal aspects of the condition. This 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 epilepsy[5]. Therefore, when AEDs fail to achieve seizure control, it is essential that the diagnosis is reviewed. It is often difficult from descriptions alone to be certain as to whether seizures are epileptic or non-epileptic. Diagnostic uncertainty is one of the major challenges a clinician has to face in managing patients presenting with apparent drug-resistant epilepsy. Psychogenic non-epileptic attacks are the main alternative possibility in this situation. 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 non-epileptic attack

disorder (NEAD) sufferers articulate the description of the seizures, compared to those with epileptic seizures[8]. 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 may be 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 will 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 Quarriers 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.

Type of event	Classification	Management
Brett's body stiffens, lips turn blue, right arm and leg may shake. Unresponsive. Usually last 1-2 minutes. Can occur repeatedly. May evolve into	Generalsied tonic or tonic-clonic seizure	If attack does not settle within 2-3 minutes, buccal midazolam 10mg 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.

Figure 1. Care plan for management of seizures and behavioural attacks in a patient with moderate learning difficulties and refractory epilepsy due to tuberous sclerosis.

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 cases[9]. 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 causes[10]. Immunotherapy may have a role in the treatment of seizures in patients who test positive for antibodies to neuronal surface 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, notwithstanding the changes to diagnostic categories introduced recently (see Figure 2 for examples).

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 epilepsies[11]. 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).

Date/Time of Appt:	18 April 2015 at 14:00
Clinic:	POOL EPILEPSY
Type of Appt:	Follow_Up
Seizure types:	Left arm, leg tonic seizure - 1-2 per day
Epilepsy classification:	Right hemispheric epilepsy secondary to low grade glioma
Medication:	Oxcarbazepine 300 mg bd, to be increased to 300 mg mane, 450 mg nocte for 2 weeks and 300 mg mane, 600 mg nocte to continue Topiramate75 mg mane, 100 mg nocte
Medical/psychiatric comorbidity:	Depression – on mirtazapine 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 themselves[12]. 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 currency[13]. 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 effects [14]. 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. This cannot be assessed without expert review of seizure semiology, epilepsy classification and imaging. This 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 horizon[15]. 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]. 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]. 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 normal[18]. 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 impairment[19].

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 profile[20]. Older AEDs, especially barbiturates, and topiramate among newer AEDs, are most likely to cause cognitive adverse effects[21]. Services of a neuropsychologist, ideally with expertise in epilepsy, can be extremely 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 in patients on long-term AED therapy. These include effects on bone metabolism, reproductive function (including sexual dysfunction, contraceptive 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 AEDs[22]. Valproate, which is a hepatic enzyme inhibitor, constitutes a special case when it comes to metabolic effects[23]. 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 the patients.

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