Advances in epilepsy

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Advances in understanding of both the causes and consequences of epilepsy have been paralleled by a number of recent reports and clinical guidelines highlighting the complexities involved in both diagnosing and treating epilepsy. We review recent developments, including comments on the evolution of clinical guidelines, anti-epileptic drugs, epilepsy surgery and new treatment approaches in development. Epilepsy genetics and emerging evidence on mechanisms of drug resistance in epilepsy will also be discussed. Issues with respect to pregnancy and epilepsy are considered, together with more recently identified dilemmas including bone health in epilepsy and whether seizures themselves cause brain damage. Imaging in epilepsy has recently been reviewed elsewhere, and will not be discussed.

Introduction

Epilepsy is the most common serious neurological disease, affecting approximately 1 in 200 people in the UK, and with an annual incidence of approximately 50–80 in 100 000. Onset can occur at any age, although is most common in the young and the old, with an increasing incidence in those aged >60 years.\(^1\) Epilepsy has been an area of great interest in the medical community since the late nineteenth century, but interest has rapidly expanded over the last 30 years, with the introduction of newer anti-epileptic drugs (AEDs), advances in molecular genetics and cell biology, and refined clinical classifications. Neuroimaging in epilepsy has played a major role in several contexts, but has recently been reviewed in this journal\(^2\) and so will not be covered again here. This article will summarize some of the other clinical and preclinical issues that have emerged in the past 5 years.

Clinical epilepsy

Guidelines

The National Institute of Clinical Excellence (NICE) guidelines on diagnosis and management of people with epilepsy have recently been...
published; a consensus statement on the treatment of people with epilepsy [published by the Royal College of Physicians of Edinburgh (RCPE)] covers broader issues of diagnosis and management, and the Scottish Intercollegiate Guidelines Network (SIGN) have updated their advice on the treatment and management of adults with epilepsy, with a paediatric version in development. These publications have been catalysed by reports from the Clinical Standards Advisory Group (CSAG) and the Chief Medical Officer (Sentinel Audit), highlighting serious deficiencies in epilepsy care. All adhere to the same broad principles: the diagnosis of epilepsy should be timely, made by a specialist and regularly reviewed, targeted services should be provided for special groups (including women and those with learning disabilities) and policies should exist for the treatment of specific epileptic conditions (such as status epilepticus). It is generally agreed that syndromic classification should also be undertaken, where possible, to guide prognosis and specific treatment decisions. In this context, all new patients should have an electroencephalograph (EEG) within 4 weeks, and magnetic resonance imaging (MRI) is recommended for most localization-related and adult-onset epilepsies (although in the acute setting CT may be preferable, largely for logistic reasons). There is debate about what constitutes an epilepsy specialist: traditionally, any consultant neurologist would be considered an epilepsy specialist, but with increasing subspecialization, some may lack recent epilepsy experience or training. There is also recognition that others, including some learning disability psychiatrists and paediatricians for example, are at least equally experienced and may have undergone targeted training in epilepsy. Most agree that any doctor with specific training in epilepsy, who monitors his or her performance and who spends a significant part of his or her time seeing patients with epilepsy should be regarded as a specialist in the field.

Anti-epileptic drug treatment

There are now 18 drugs licensed in the UK for the control of epileptic seizures, with new agents appearing at the rate of approximately one per year over the last 10 years. Against this background the choice of which AED to use has become ever more confusing, even for the dedicated epileptologist. A technology appraisal issued by NICE reviews the use of anti-epileptic medications based upon the evidence and cost implications to date, and specifically considers whether (or when) newer, less tested and invariably more expensive drugs should be used instead of the older more established drugs (carbamazepine and sodium valproate). NICE concludes that, for most patients, treatment with the older AEDs should be considered first, unless there are good reasons to consider otherwise,
such as potential drug interactions, poor tolerability or hypersensitivity with older drugs, or in women of child-bearing age. Beyond this they make no specific recommendations, except for the exclusion of phenytoin as first-line treatment, other than in the management of status epilepticus. RCPE and SIGN are in broad agreement. The changing role of phenytoin in the long-term treatment of epilepsy almost certainly reflects its pharmacokinetics, high risk of drug interactions, and relatively poor tolerability, but in our experience this is not yet reflected in practice. A large multicentre study comparing standard and new AEDs in new-onset epilepsy (SANAD) has recently completed recruiting, and it is hoped that it will provide more robust data to guide initial treatment decisions in the future.

Initial treatment will result in \(~\)50% of patients being rendered seizure free on the first medication prescribed, with a further 20% achieving seizure freedom with the second medication and \(~\)30% being refractory.\(^9\) Whether to add or substitute a second drug, and what drug or combinations of drugs to use, are more difficult questions. The published guidelines all agree that monotherapy is preferable for most patients, and where the first AED fails, another should be substituted, although the evidence to support this approach rather than early add-on treatment is largely lacking.\(^10\) Most clinicians accept that polytherapy is of benefit for the significant subgroup of the epilepsy population who are drug resistant, and will commonly maintain a backbone AED to which patients have partially responded with serial trials of add-on therapies. It is important to have realistic expectations at all stages when considering add-on therapy, and in general where a drug has not helped it should be withdrawn. All are effective in partial epilepsies, but only a few of the newer AEDs (topiramate, levetiracetam and lamotrigine) appear so in primary generalized syndromes. In considering newer AEDs, the experience with vigabatrin, one of the more efficacious agents, but with a serious irreversible side effect (visual field defect) becoming apparent only some years after licensing,\(^11\) inevitably means that patients should be advised that there may be as yet unidentified and unexpected side effects, however unlikely. Beyond these basic principles, at present there is insufficient evidence on which to base specific treatment choices. Meta-analysis of published trials broadly supports clinical practice,\(^12,13\) suggesting that some AEDs (e.g. topiramate, levetiracetam) may be more efficacious than others, with lamotrigine, levetiracetam and gabapentin perhaps better tolerated. Based on this it seems intuitive to consider the more ‘tolerable’ drugs for patients in whom the problem is primarily unacceptable side effects, and the ‘stronger’ ones when seizure control is the priority. Some have promoted so-called ‘rational polytherapy’, based on the principle that AEDs with different mechanisms of action are more likely to complement each other.\(^14\) However, the data are preliminary,
and the multiple mechanisms of action of many AEDs make this observation complex. To date there is no good evidence to support specific drug combinations. In this context, the recent identification of the binding site of leviteracetam, SVR2A, is of interest.\textsuperscript{15} This receptor is believed to be involved in synaptic vesicle formation/function, and thus the release of neurotransmitters, and therefore may represent a new mechanism of action. This offers exciting prospects for understanding the mechanisms of epileptogenesis and future drug discovery.

The mechanisms by which some patients are resistant to AEDs are also slowly being unravelled. Building on work in cancer, it is now understood that one of the mechanisms that operates in drug resistance is the active transport of drugs (including many conventional AEDs) away from the epileptogenic site. These drug transport proteins, including P-glycoprotein, MRP1 and MRP2, have been found in animal studies to be upregulated following status epilepticus and kindled seizures. Human evidence includes similar changes in surgically resected epileptogenic tissues (e.g. hippocampal sclerosis, dysembryoplastic neuroepithelial tumours and focal cortical dysplasia) and in studies of genetic polymorphisms in drug-resistant compared with drug-sensitive patients.\textsuperscript{16} These very recent advances have yet to translate into useful clinical practice, but it is hoped that increasing understanding of the mechanisms of drug resistance may open new avenues in treatments in the future.

Finally, other novel treatment approaches for refractory patients, including focal drug delivery and stem cell grafting, are now being investigated in animal models,\textsuperscript{17} some of which may be appropriate for clinical studies within the next few years.

\textbf{Epilepsy and pregnancy}

It is well established that, in the pregnant patient, all AEDs carry a potential risk to the unborn child, but it is only recently with prospective national and international pregnancy registers that reliable data on both the newer and older AEDs are emerging. UK results are broadly consistent with others,\textsuperscript{18} confirming that for most women the risks of major malformations are small, although approximately double the background risk. Regarding the newer drugs, there is sufficient information to draw conclusions only for lamotrigine, which appears to be one of the safer AEDs in pregnancy (as has traditionally been the case for carbamazepine). Valproate appears to carry slightly higher risks than the other AEDs (Figure 1), forming the basis of the guidelines from the Chief Medical Officer and NICE that alternatives should be considered in women of child-bearing age if possible. The possible consequences of \textit{in utero} AED exposure on cognitive development have also received
much attention. Following a preliminary report of increased special educational needs (used as a surrogate marker for learning disability) in children exposed \textit{in utero} to valproate monotherapy or polytherapy, compared with unexposed children or other AEDs, a more robust follow-up study on the same children has now been published.\textsuperscript{19} This reports lower verbal IQs associated with valproate exposure, even after adjustment for some, though not all, potential confounders (such as maternal IQ or epilepsy type). However, the study population was identified using a retrospective postal questionnaire and had only a 40% response rate; thus there is obvious potential for selection bias, and the numbers are too small to draw confident conclusions for some of the subgroup analyses. Notably, convulsions during pregnancy also emerged as being associated with poor outcome in the child. Given that for some women valproate may be the only drug that effectively controls their seizures,\textsuperscript{20} the choice of AED in pregnancy is not straightforward and there are many questions still to be answered. Certainly women facing this dilemma should be advised not to stop their medication without seeking medical advice, and individual counselling to help them make an informed decision is required, although absolute risks are difficult to give in most instances.

\textit{Bone health}

It is increasingly recognized that epilepsy patients are at increased risk of osteopenia and osteoporosis. This is commonly ascribed to long-term
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AED treatment, but attributable risks have not been clearly established. There are numerous other confounders such as diet, exercise, and genetic susceptibility, independent of epilepsy, and much of the work has been conducted on refractory patients or those in long-term care, where these factors undoubtedly interact. In a recent study of 81 men attending an epilepsy outpatient clinic, age and length of time on AEDs were independent risk factors for reduced bone mineral density (BMD). A cross-sectional study showed that patients with epilepsy have lower BMD and vitamin D levels, but that the vitamin D levels were independent of BMD. Generalized seizures, multiple AEDs and enzyme-inducing AEDs were all associated factors. However, the sample was only partly representative; more patients had uncontrolled seizures than in the normal population, and control values were from a standard database rather than an age-matched cohort. It seems clear that there is an association between epilepsy and osteoporosis, but what proportion of the additional risk is drug related or when the treating clinician should consider either dual-energy X-ray absorptiometry (DEXA) scanning or preventative treatment in epilepsy patients is not established. Until these questions are answered, it seems prudent as a minimum to make all patients aware of general bone health issues, and to offer screening/treatment to those at especially high risk (e.g. post-menopausal women, in long term residential care). More stringent guidelines have been proposed, but are not yet widely accepted.

**Sudden unexplained death in epilepsy**

Patients with epilepsy have a higher mortality than the general population, with a standardized mortality ratio of 1.3–9.3%. Some of this is related to underlying disease (tumours, strokes etc.), but the most common epilepsy-related deaths are suicide and sudden unexpected death in epilepsy (SUDEP). In the UK it is has been estimated that ~800 people die each year during or shortly after a seizure, and that ~40% of these deaths in adults and ~60% in children are potentially avoidable. SUDEP accounts for 18% of all epilepsy-related deaths, with an annual incidence of <1 in 1000 in the general epilepsy population, rising to 1 in 100 in refractory patients awaiting epilepsy surgery. Identified risk factors include frequent (tonic–clonic) seizures, treatment with more than one AED, frequent changes of AED, IQ <70 and long duration of disease. Because SUDEP is definitively unexpected, it is difficult to investigate the cause of death. It has been suspected for some time that autonomic disturbance leads to either asystole or profound hypopnoea, and there is evidence to support both of these hypotheses. A retrospective study of ~1400 patients admitted for video-telemetry revealed five
cases of asystole, lasting for up to 60 s in one case.\textsuperscript{27} Another group investigating the basic mechanisms of seizure-related death demonstrated significant changes in the respiratory pattern of rats in response to seizures induced by subcutaneous pilocarpine.\textsuperscript{28} Finally, evidence that SUDEP is a seizure-related phenomenon is supported by work showing that there is evidence of early neuronal injury in the form of neurons stained positive for HSP-70 and c-Jun, two reliable and specific markers of acute neuronal injury, in the hippocampi of patients dying of SUDEP compared with the hippocampi of controls.\textsuperscript{29} This contrasts with previous work, which had failed to demonstrate an association between SUDEP and more conventional markers of damage, such as cell loss, and indicates that there is a ‘neurological insult’ prior to death, although whether this is directly related to seizure activity or is an epiphenomenon, secondary to other physiological compromise, is unclear.

**Non-medical management**

**Surgery**

Around 30\% of patients with epilepsy cannot be rendered seizure free with currently available AEDs. Surgery is an established option for those with lesion-associated epilepsy (neoplastic lesions, vascular malformations) or certain types of temporal lobe epilepsy (TLE). Recent studies have clarified important factors in selecting the most suitable patients, including a clearly defined structural focus and a history of partial seizures.\textsuperscript{30} Functional imaging may be helpful in patients with negative structural MRI, where non-morphological abnormalities are strongly lateralized to the same side as the EEG abnormalities,\textsuperscript{2} as well as offering a potentially less invasive tool than the traditional amytal (or WADA) testing for the preoperative assessment of language and memory lateralization. However, for the most part, this is still very much a research tool.

There has been one important randomized controlled trial comparing epilepsy surgery with continued medical management, which clearly demonstrated superior efficacy and tolerability for surgery.\textsuperscript{31} Fifty-eight per cent of patients with refractory temporal lobe seizures arising from hippocampal sclerosis were seizure free following surgery, compared with very few (<5\%) with trials of various AEDs. The same conclusions have been reached in a meta-analysis of this and other evidence.\textsuperscript{32} We also know that, in experienced hands, epilepsy surgery is safe. In a large Swedish population-based study there were 3.4\% (8.9\%) major (minor) post-surgical complications and the mortality rate was 0.3\%, substantially lower than the risks of living with intractable epilepsy for a long
period of time. Surgery is also cost effective, and financial savings may be made if patients are carefully selected, especially if the long-term non-medical costs of uncontrolled epilepsy are also taken into account. However, at present there are only just enough neurosurgeons in the UK to manage the incident cases requiring surgery, without even touching the ‘pool’ of prevalent cases. Clearly, when the resources required for adequate evaluation of potential cases (neuropathology, neuropsychology, neuropsychiatry, epileptologists, specialist nurses) are also considered, this situation needs addressing sooner rather than later when considering epilepsy service provision and workforce planning.

The traditional surgical management of TLE has been anterior temporal lobectomy. Some centres are perfecting a more selective approach (involving excision of the amygdala and hippocampal structures alone) and reporting similar outcomes to the traditional procedure, although there are no controlled studies examining this. Less destructive techniques such as multiple subpial transection (MST) are sometimes considered for lesions in eloquent brain areas where resection is inappropriate. In selected cases, MST (with or without resection of the lesion) leads to >95% reduction in 62–68% of simple and complex partial seizures and in 71–87% of generalized seizures. However, 19% of patients with pure MST and 23% with additional lesional resection had persistent new neurological impairment, and 15–20% of patients report increased simple partial seizures after the procedure. Thus the risks need to be carefully balanced against any potential benefit, and this procedure should only be undertaken in experienced centres.

**Vagus nerve stimulation**

The US Food and Drug Administration approved vagus nerve stimulation (VNS) for use in 1997, and its application to medically intractable epilepsy is also developing in the UK. A stimulating electrode is attached to the mid-cervical portion of the left vagus nerve, powered by a pulse generator implanted in the chest. Three-year follow-up details are available for over 400 patients, with effective seizure reduction (~40%) in all seizure types for up to 3 years. In general VNS appears very well tolerated, with 72% continuation at 3 years and ~50% of withdrawals due to lack of efficacy. The main complications are paraesthesia, cough, and hoarseness. Many studies also report a reduction in overall AED burden, and corresponding improvements in alertness and general well-being. However, in interpreting these results, it must be remembered that VNS has been used as a last resort for most patients included in the study, which may influence retention figures. The costs involved are also not inconsiderable, both for the device and specialist
follow-up. Nonetheless, it is clearly a useful option for some patients with refractory epilepsy.

**Basic science**

**Genetics**

It has long been recognized that epilepsy can be familial, ranging from siblings with primary generalized syndromes to encompass the many strongly genetic conditions, such as tuberous sclerosis or progressive myoclonic epilepsies, in which epilepsy may be a symptom.39

Generalized epilepsy with febrile seizures plus (GEFS+), first described in 1997,39 is perhaps the best described familial epilepsy syndrome. This autosomal dominant syndrome includes varied phenotypes, ranging from simple febrile seizures (that may persist beyond the age of 6 years) to afebrile generalized seizures and, at the severest end of the spectrum, myoclonic astatic epilepsy and Dravet’s syndrome (severe myoclonic epilepsy of infancy). The phenotypic variability even within one family/gene is large, and in the larger GEFS+ pedigrees the entire range of variants can be seen, reflecting the fact that, although it is principally a monogenetic disorder, other factors are influencing the phenotype (environmental influences, genetic polymorphisms, etc). Four genes have been identified so far in the GEFS+ syndrome; three (SCN1A, SCN2A and SCN1B) code for sodium channels, and one (GABRG2) codes for a subunit of the gamma amino butyric acid (GABA) A receptor. All of them render neurons more excitable. Other gene mutations have been identified in potassium channels (KCNQ2 and KCNQ3) associated with benign neonatal familial convulsions, and in the nicotinic acetylcholine receptor (CHRNA4 and CHRNB2) in autosomal dominant temporal lobe epilepsy.

There are also gene mutations not encoding for ion channels, including the LGI1 and ARX genes in autosomal dominant partial epilepsy with auditory features and X-linked myoclonic epilepsy with spasticity and intellectual disability, respectively.39 These are proteins involved in cell migration during development, but the exact mechanisms by which these genes exert their effects are unknown.

Many patients satisfy the clinical criteria for a particular syndrome, but do not possess the appropriate genetic abnormalities (e.g. only 30–50% of patients with Dravet’s syndrome possess an abnormality of the sodium-channel gene). Similarly, the mutations identified above have not been readily demonstrated in the more ‘common’ epilepsies. When genetic analysis became possible, there were great hopes that it would clarify the mechanisms of epileptogenesis, seizure generation and propagation,
leading perhaps to novel treatments. Unfortunately, as we acquire more knowledge, it seems increasingly likely that epilepsy is a ‘convergent’ response to many basic malfunctions of brain activity or development. Genetic variation must play a role, perhaps in terms of a general seizure susceptibility and in responses to external insults such as head injury, but it seems that complex interactions are involved. Greater genetic understanding generates new questions, and may even lead to new treatments, but it is a long way from providing useful prognostic or clinical information for the individual.

Do seizures damage the brain?

That seizures can cause damage is well established from experimental models of status epilepticus (SE), in which cell death is observed in the dentate gyrus and the CA1 and CA3 regions of the hippocampus, a pattern which resembles hippocampal sclerosis. These changes are independent of the systemic compromise associated with SE, are associated with behavioural and memory deficits, and are thought to be a direct result of the seizure activity via excitotoxic mechanisms potentially involving mitochondrial dysfunction, free radicals and inflammatory changes. Biochemical studies suggest that abnormalities persist up to 44 h beyond the duration of the seizures themselves, offering a clinically relevant therapeutic window for neuroprotective intervention if the mechanisms can be sufficiently unravelled. There are numerous other changes at a cellular level such as neurogenesis and loss of interneuron subclasses, some of which have been detected following even a single kindled seizure in rats. The challenge is to separate the damaging from the compensatory and to establish which particular changes are associated with important clinical outcomes such as cognitive impairment or the development/worsening of epilepsy.

Human data, although lacking in comparison and inevitably confounded by other factors, broadly supports that seizures can, at least in some instances, cause brain damage. MRI series following SE have confirmed progressive hippocampal atrophy, although the numbers of patients are small. A recent post-mortem report from a patient with 5 months of intractable seizures after SE, with no documented systemic compromise or other cause, also reported typical hippocampal damage, in keeping with a handful of earlier studies.

The question of whether SE itself can cause epilepsy also arises, and epidemiological and case series data in this area have recently been reviewed, without firm conclusions. Approximately 12% of all cases of epilepsy have SE as their first manifestation, although clearly this does not exclude the possibility that whatever caused the SE might also
predispose to later epilepsy. Similarly in humans, whilst up to 80% of patients with hippocampal sclerosis have experienced febrile convulsions, few infants with febrile convulsions will develop epilepsy. Nonetheless it remains unclear whether the long duration of the initial seizure is causal or represents an already established predisposition to epilepsy. Experimental studies suggest that SE at least can cause later epilepsy, and many animal models of epilepsy (electrical and chemoconvulsant) rely on one episode of limbic SE being followed by recurrent unprovoked seizures days or weeks later. The fact that animals which do not enter SE are less likely to experience further seizures suggests that the seizure activity in itself is relevant to later epileptogenesis, although unless genetically identical animals are used (rarely the case), the possibility that some animals are inherently more susceptible to both severe SE and later epilepsy remains.

Only a minority of patients with epilepsy experience SE, but ~30% of the prevalent population have ongoing seizures that are resistant to medication. Thus a further important area in this context is whether recurrent brief seizures cause damage, in the same way that it appears that SE can. Refractory epilepsy is associated with significant psychological morbidity, as recent studies have continued to highlight, including problems with memory, personality change and psychiatric illness (including psychosis). However, whether this reflects accumulated neuronal loss and dysfunction secondary to seizures, a progression of underlying disease or other confounders (including AED effects) is not clearly established. Animal studies support the relevance of seizure-induced neuronal loss/dysfunction, even in the absence of status epilepticus. Rats experiencing brief recurrent seizures, using the kindling model, show impaired memory and have reduced cell density and neuronal numbers in the hippocampus ex vivo. In humans, some case series of patients experiencing frequent seizures have reported decreased hippocampal volumes over time, but this is not a universal finding. Cross-sectional studies have shown that patients with higher frequency of seizures, prolonged seizures and febrile convulsions are more likely to have hippocampal sclerosis, but it is still unclear whether the morphological changes are secondary to the seizures themselves or to other factors (such as hypoxia or head injury sustained ictally), or represent cause rather than effect.

There are several potential explanations for the conflicting reports in humans thus far. It may be that much of the work, concentrating to date on hippocampal structures and function, is missing changes elsewhere in the brain. An important prospective longitudinal MRI study has convincingly shown that there is generalized neocortical atrophy, over and above age-related changes, in the brains of patients with chronic epilepsy when compared with those with newly diagnosed epilepsy and normal controls. Alternatively, the apparently conflicting results may
reflect a subgroup of patients sensitive to the effects of frequent seizures. If this were the case, then a way of identifying these patients early in the course of their disease would allow us to develop and use novel neuroprotective strategies, complementing current treatments that (at present) only suppress seizures. For patients, it seems that seizure can sometimes damage the brain, and this is a further reason to aim for maximal seizure control where possible. How often and significant such damage is, and thus what clinical importance this has for most patients with epilepsy is as yet unknown.

**Conclusion**

For patients, clinicians and researchers in epilepsy, this is a rapidly changing field, but one offering the promise of novel treatment approaches, increased understanding about the causes and consequences of epilepsy, and, it is hoped, a greater number of seizure-free patients with a better quality of life. It has long been recognized that epilepsy is not a single disease, and thus it is not surprising that, despite massive developments in recent years, no panacea amongst the new drugs has emerged. The need for syndromic classification, in both clinical practice and research, is now clear in order to make progress in tailoring treatments to individual patients. The recent clinical treatment guidelines provide a benchmark for current practice and represent consensus on what the standards of care should be, although service and manpower constraints require major developments to make them achievable. We still have a long way to go in addressing the fundamental questions relating to seizures and brain damage, the mechanisms and identification of drug resistance, and the epileptogenic process itself, but exciting times are ahead.

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