Evolution Not Revolution: epilepsy in the last ten years

The new millennium ushered in the age of communication and ACNR has spearheaded high-quality, accessible neurology. As a keen new consultant, I was delighted to be asked to write a series of articles about various aspects of epilepsy. Now ten years on, the editors in their desperation have charged me with looking back at epilepsy and asking what’s new: acorns, green shoots or grand oaks? There follows an unapologetically personal and perhaps hugely biased mosaic of those areas which have stuck in my mind.

I was grabbed by the identification of fast ripples (100-500Hz) described in animals and then in human intracranial EEG studies described as "field oscillations composed of hypersynchronous action potentials" possibly mediated via gap junctions, rather than synapses. Ripples may precede the onset of a seizure by a considerable period of time and are blocked by inhibitors of glutamate. They open a new vista in consideration of epilepsy mechanisms and treatment, which has yet to be realised and this reflects the core theme of my article; that, to date, our treatments deal with seizure expression, and not root causes. Of course, the most powerful tool we currently have to look into causes is genetics. Monogenic epilepsies (Table 1) have been identified, starting with autosomal dominant frontal lobe epilepsy (ADNFLE). Most of these monogenic epilepsies are disorders of ion channels or neurotransmitters, which is reassuring when considering the mechanisms of action of all the anti-epileptic drugs we possess. We have known since the work of William Lennox over half a century ago that there is a strong genetic component to epilepsy, even if NHS coffers are considerably emptier. So what do the new drugs offer? A few patients have become seizure-free who would never have been seizure-free before. Some patients have fewer or milder seizures. We can now achieve similar results with fewer adverse effects, less drug interactions and simpler pharmacokinetics. Why AED all-too-frequently do not work has also been the subject of investigation than environment and the clearest example of their interaction is the doubling of the risk of epilepsy in those with a major head injury who also have a family history of epilepsy.

There has been a burgeoning of anti-epileptic medications in the last ten years. But my guess is that, if you are as full as ever it was, even if the NHS registers, has given us the first robust and clinical-quality data showing that lamotrigine, of the AEDs tested, had the highest retention rate in prospective data on about half of pregnant women and genes can be tested quickly. I hope that, if I am asked to write another article in another ten years, the answer will be very different. Even with monogenic disorders, mapping clinical syndrome to gene defect has not proved altogether straightforward, with significant heterogeneity and a "many-to-many" map. So what influences the variable expression of genetic abnormalities? In some disease it may be the type of genetic abnormality; deletion or point mutation or the locus within the gene or else presumably other variable genes playing a part.

Even now that we know more about ion channels they are becoming predictably more complex. In neonates GABA is an excitatory neurotransmitter – who would have guessed that? This and other maturational changes, including the progressive myelination of the young brain, may go some way to explaining why childhood epilepsy is such a different disease to adult epilepsy and with all those strange disorders that no self-respecting adult neurologist can ever remember. In ADNFLE, seizures may result in a gain in inhibition in a homozygous mouse model. So a traditional view of drugs as uppers and downers of cortical activity, whilst appealing, is clearly simplistic and what may be important is the role of the neurotransmitter in neuronal synchronisation in the light of modified anatomy and physiology. Identifying the gene is only one step, moving on to determining pathophysiology in different patients with different presentations and designing effective and safe drugs, is quite another. The next phase will be slower but therapeutically more rewarding. Genes may be tricky but are perhaps easier to investigate than environment and the clearest example of their interaction is the doubling of the risk of epilepsy in those with a major head injury who also have a family history of epilepsy.

Mark Manford
Trained in neurology at the National Hospital where he obtained his MD researching into clinical patterns of epilepsy, and at the Wessex Neurological Centre. He has been a Consultant Neurologist at Addenbrooke’s and Bedford Hospitals since 1997 and has continued his interest in epilepsy, including writing a greatly under-rated textbook on the subject. He is also extensively involved in undergraduate medical training in Cambridge.

Correspondence to:
Email: mark.manford@oneservice.co.uk
and valproate are statistically significant to date and whilst reassuring in the case of the first two, valproate emerges as the bad boy on the block. This combined with preliminary data suggesting that the verbal IQ of children exposed to valproate in utero may be reduced,

1 is a major cause of concern for a drug which may be the only option for some women with, for example, severe juvenile myoclonic epilepsy.

When treating our refractory patients, it is as well to bear in mind studies suggesting that the main determinants of quality of life are related to depression and adverse effects of medication and not to seizure frequency.10 Poring over a seizure diary to see if seizures have been reduced by 35% or 50% is of little relevance to many patients but it is the measure used in regulatory studies prior to drug marketing. Smarter studies would be helpful but this needs a change in regulatory requirements. Sometimes the most important manifestation of a disease is not the most obvious; Parkinson’s disease doctors have learned to think about non-motor manifestations and epilepsy doctors must consider their co-morbidities. Some new ones have gained prominence in the last ten years, in particular new memory disturbances such as accelerated forgetting;10 the tendency for memories to drop out over a few weeks, which is not detectable in the short time frame of standard psychometric testing and transient epileptic amnesia,11 which has some similarities to transient global amnesia, some women with, for example, severe juvenile myoclonic epilepsy.

The approach to treatment is maturing, particularly in epilepsy patients who develop drop death in epilepsy, long recognised but underestimated is now given the prominence it deserves, thanks largely to the efforts of the charity “Epilepsy Bereaved” and although I still do not know the right way of handling the issue, it is something at the forefront of my mind. Investigation of epilepsy mortality has led to a practical change with a regular search for and occasional discovery of seizure-induced cardiac arrhythmia, particularly in epilepsy patients who develop drop attacks.12 High quality structural imaging continues to provide new insights into epilepsy.13 A more powerful magnet (3T) may find structural abnormalities in 20% of patients with normal standard imaging and voxel-based morphometry can identify subtle changes, not obvious on standard imaging. The neurophysiology purists argue that conventional imaging looks at structure and epilepsy is a disturbance of function, but new methods such as diffusion tensor imaging and tractography may identify changes in connectivity which may be of significance in a disorder which is a disturbance of networks. Tractography is also of value in presurgical evaluation for temporal lobectomy, determining the location of Meyer’s loop and so being able to predict those patients more at risk of visual field defects.14 But the approach is multifaceted and even in patients whose structural MRI is normal, investigators have become better at identifying the region of epileptogenesis with a combination of functional imaging and neurophysiology such that successful outcomes of surgery are increasingly reported in these patients (Figure 1), although it can be argued that the definition of a normal scan depends on the type of scan used. Diffuse brain disease is also not a contraindication to surgery if it can be shown that the epilepsy satisfies conventional criteria of focal onset and good surgical outcomes can be seen in patients with apparently diffuse disorders such as tuberose sclerosis or severe learning disability and even in patients with apparently diffuse electrical abnormalities15 but focal congenital structural lesions. In malformations of cortical development, the combination of EEG, structural and BOLD MRI is helping to elucidate the relationship of the lesion to the electrical disturbance; it appears that the underlying cortex is the key player in many cases, which has implications for surgical treatment.16 So it seems that neuroimaging and EEG both have their place, neither should be over-interpreted in presurgical evaluation. The assessment of cognitive function in epilepsy is often in preparation for surgery and for half a century the Wada test has been the gold-standard but this has been

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHRNA2, CHRNA4, CHRN8B</td>
<td>Different subunits of the nicotinic acetyl choline receptor</td>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
</tr>
<tr>
<td>KCNQ2, KCNQ3</td>
<td>Neuronal voltage gated potassium channel (M current)</td>
<td>Benign familial neonatal seizures</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Neuronal voltage-gated sodium channel α1 subunit</td>
<td>GEFS+, Dravet syndrome, febrile seizures</td>
</tr>
<tr>
<td>SCN1B</td>
<td>Neuronal voltage-gated sodium channel β1 subunit</td>
<td>GEFS+</td>
</tr>
<tr>
<td>GABRG2</td>
<td>γ2 subunit of the GABA_A receptor</td>
<td>GEFS+, Dravet syndrome, febrile seizures Childhood absence epilepsy</td>
</tr>
<tr>
<td>GABRD</td>
<td>δ subunit of the GABA_A receptor</td>
<td>GEFS+</td>
</tr>
<tr>
<td>GABRA1S</td>
<td>α1 subunit of the GABA_A receptor</td>
<td>Juvenile myoclonic epilepsy</td>
</tr>
<tr>
<td>CLCN2</td>
<td>Voltage gated chloride channel</td>
<td>Various types</td>
</tr>
<tr>
<td>CACNA1H</td>
<td>Neuronal voltage gated T-type calcium channel</td>
<td>Childhood absence epilepsy</td>
</tr>
<tr>
<td>EFHC1</td>
<td>Myoclonin, function unknown</td>
<td>Juvenile myoclonic epilepsy</td>
</tr>
</tbody>
</table>

GEFS+ Generalized epilepsy with febrile seizures plus.
questioned with the development of functional neuroimaging techniques, which in some centres have taken over altogether from Wada testing and in others supplement it.21 Not without risk, distressing for the patient and difficult to interpret, even though the Wada test must be one of the most dramatic investigations in medicine, its passing is a blessing for patients.

Where drugs and resective surgery do not work, it is now commonplace for patients to be considered for palliative surgery in the form of vagus nerve stimulation. I have moved from being something of a sceptic in the technique to a modest supporter on the basis that although it does not make patients seizure-free, it probably does give a useful improvement in seizures in 25%-40% of patients and does so without the cognitive and psychiatric side effects of anti-epileptic drugs which patients find so distressing.22

So my summary of the last ten years is that we do what we always did and I think we do it a little better and more sensitively with a growing understanding of what is tediously called patient-focussed (otherwise known as good) practice, but we have not had any quantum leap in understanding, which would really allow us to make inroads into the enormous psychosocial morbidity of uncontrolled epilepsy, still the commonest serious neurological disease. We have many new strings to our pharmaceutical bow but we need a new instrument. Where Alzheimer’s disease modifying drugs are around the corner and MS disease modifying drugs are with us already, epilepsy disease modifying drugs don’t even know where the bus-stop is. So my hopes for the next ten years firstly, not another drug that controls seizures by blocking electrical activity, although a really good one would do no harm, but one that interferes with epileptogenesis that we can give patients after major head injuries, encephalitis and haemorrhages, which we know carry a high risk of later epilepsy. Arguably we may have filled in some gaps in the picture left to us by Hughlings Jackson over a century ago but our conceptual framework has advanced only a little and my second hope is of increasing knowledge of the mass action of neurons, what makes them synchronise into pathological networks and how we can interfere with that process. Hopefully knowing the genes will start to inform what goes on inside cells as well as on their surfaces. We need to treat epilepsy and not just seizures. Finally we need to keep doing epidemiological studies, because without knowing the natural history of the disease we are treating, we are navigators without a map.

REFERENCES

17. Tayoka T, Sakamoto M, Nakagawa H. Diffusion tensor tractography of the Meyer Loop in cases of temporal lobe resection for temporal lobe epilepsy: correlation between postsurgical visual field defect and anterior limit of Meyer Loop on tractography. AJNR 2008;29:1339-34.
18. Tyvaert L, Hawoo C, Kobayashi E et al. Different structures involved during ictal and interictal activity, although a really good one would do no harm, but one that interferes with epileptogenesis that we can give patients after major head injuries, encephalitis and haemorrhages, which we know carry a high risk of later epilepsy. Arguably we may have filled in some gaps in the picture left to us by Hughlings Jackson over a century ago but our conceptual framework has advanced only a little and my second hope is of increasing knowledge of the mass action of neurons, what makes them synchronise into pathological networks and how we can interfere with that process. Hopefully knowing the genes will start to inform what goes on inside cells as well as on their surfaces. We need to treat epilepsy and not just seizures. Finally we need to keep doing epidemiological studies, because without knowing the natural history of the disease we are treating, we are navigators without a map.

Figure 1: A 38-year-old right-handed woman who underwent resective surgery for chronic intractable complex partial seizures and secondary generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality [A]. Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality (A). Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality (A). Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality (A). Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased and secondarily generalised tonic-clonic seizures.