Clinical advances in the understanding, diagnosis, and treatment of epilepsy

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In the last decade, there have been tremendous advances in our understanding, diagnosis, and treatment of epilepsy. These have included: insights into the mechanisms and biomarkers of sudden unexpected death in epilepsy; a growth in our understanding of the genetics of epilepsy; the role of somatic mutations in malformations of cortical development; advances in EEG analysis for seizure detection and prediction, and the teratogenic potential of antiseizure drugs. This issue has set out to address a separate set of equally important topics, many of which address questions or comments that I commonly hear in my clinic.

Two particular qualities of seizures that have an enormous clinical impact are their randomness and associated impairment of consciousness. The apparent randomness of seizures means that, even when people are having infrequent seizures, the seizures still have a significant impact on quality of life. This is because the threat of seizures hangs there like the sword of Damocles, poised to fall at any moment. However, many patients assure me that their seizures are not completely random and that they occur at certain times of the year or on a monthly basis (this is so for both males and females). In this issue Baud et al. (xx-xx) provide growing evidence that these patients are correct, and that seizures are not completely random events, but occur in cycles of different lengths (circadian, weekly, monthly and seasonally). Determining these cycles in individual patient may give us insights into the mechanisms underlying seizure initiation and also a means to improve seizure prediction and timed interventions.

Impairment of awareness during seizures has a considerable influence on the impact of seizures, and consequently is a critical component in seizure classifications. Lambert and Bartolomei (xx-xx) have provided a thought-provoking review into quantification of consciousness (a significant clinical challenge), and recent insights into the mechanisms by which seizures may influence cortical networks and so impair consciousness. They conclude with a discussion on how these insights have led to studies in brain stimulation which may prevent or ameliorate impairment of consciousness. These studies are relevant beyond epilepsy and give us an appreciation of mechanisms that maintain conscious and conscious thought important for many clinical situations (in particular traumatic brain injury).

Trivisano and Specchio (xx-xx) discuss an equally important and challenging area – that of epileptic encephalopathies. These are severe conditions in which epileptic activity is proposed to lead or contribute to a progressive disruption of cerebral function and delayed development. These conditions raise an important question – is it the epileptic activity that causes the developmental delay or is there an underlying brain disorder that separately results in developmental delay and a severe epileptic phenotype? It is increasingly recognised that this should not be a binary question; rather, epileptic activity and the underlying brain disorder contribute to different degrees to developmental delay depending upon the aetiology. For most conditions, it is likely that severe epileptic activity exacerbates aetiology-driven cognitive and behavioural problems. Greater insight into the separate roles of epileptic activity and aetiology will, undoubtedly, better inform treatment of these devastating conditions.

There has been an enormous growth in the number of new drug treatments available for epilepsy in the last 30 years, giving the illusion that epilepsy must now be a condition that we can almost always successfully treat. In a sobering review from Chen et al. (xx-xx), they provide the evidence that efficacy and tolerability of antiseizure drugs has not improved over the last 30 years and that antiseizure drug resistance is as great a problem today as it was in the past. There have, however, been some benefits including improved drug-drug interactions and possibly decreased teratogenic potential. Also, there are differences in the incidence of less severe adverse effects between the older and newer antiseizure drugs. In addition, they discuss the use of drugs for specific indications (most recently cannabidiol for

Dravet and Lennox-Gastaut syndrome), and indeed, the growth in new drugs and a greater understanding of the epilepsies may, in the future, permit rational prescribing of specific drugs for specific epilepsies or aetiologies, as a move towards a more personalised approach to epilepsy treatment.

There have been growing concerns about the interaction of epilepsy and dementia – do antiseizure medications or epilepsy increase the chance of dementia? Beghi and Beghi (xx-xx) address this important question, but first, they make the important point that dementias are one of the commonest causes of seizures and epilepsy in the elderly, and with the growing prevalence of dementia, this is becoming of greater importance. Epilepsy, itself, can also be associated with cognitive decline but this is multifactorial with some recent evidence indicating that there may be shared pathways between epilepsy-related cognitive decline and dementia. They review the evidence of the association of antiseizure drugs and dementia and conclude that they are not associated with the development of dementia but that the drugs themselves can have an impact on cognition and this is probably less so with the newer antiseizures drugs.

For those with drug-resistant epilepsy, resective epilepsy surgery is the most effective treatment; however, few people with drug-resistant epilepsy are suitable. In an excellent review of recent studies, Frauscher (xx-xx) discusses the state of the art in presurgical investigation. In particular, the role of advanced analysis of neurophysiological measures looking at seizure spread and seizure networks to gain a better indication of the region that needs to be resected. Advances in analysis of presurgical data along with advanced computational methods (in particular artificial intelligence) will, in the future, give us better and less invasive ways of determining the areas that need resecting and of predicting outcome. This will translate to more effective epilepsy surgery that will be available to a larger number of patients.

Epilepsy surgery, however, comes at a cost, and one of the key components of this is the cognitive cost of epilepsy surgery reviewed by Baxendale (xx-xx). This is a concern of patients and should also be the concern of the physician. The extent of the risk depends upon not only the surgical procedure but also patient factors such as age, duration of epilepsy, seizure type and frequency, other comorbidities and presurgical cognitive function and reserve. As is pointed out in this critical article, there are web-based tools available to help determine cognitive risks, and discussion and calculation of these risks are now necessary requirements of any presurgical epilepsy assessment.

Epilepsy research continues to advance apace, and the challenge now is to translate many of these advances into improvements in epilepsy care and treatment. The articles in this issue hopefully give an insight into research that is being undertaken into questions that are pertinent to people with epilepsy and that will hopefully lead to improvements in the management of this potentially devastating condition.

Acknowledgement

MCW receives support from the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Conflicts of Interest

MCW has received honoraria, consulting fees and/or research grants from Vitaflo, UCB Pharma, Eisai, Sage, Special products and Marinus