Epilepsy in the 21st Century

Epilepsy research has evolved substantially over the past 20 years. Advances have been made in the taxonomy and pathogenesis of seizures and epilepsies as well as seizure onset and propagation, genetics, and acquired causes of epilepsy. There have been improvements in seizure detection, medical treatment, brain imaging, and outcomes of surgery.

The classification and taxonomy of epileptic seizures and epilepsy syndromes has evolved over the past two decades, with an improved understanding of the underlying causes and associated risk factors. After the seizure type has been classified, epilepsy is categorised as focal or generalised, or both, or unknown. If possible, an epilepsy syndrome is then defined, primarily on the basis of risk factors or aetiology, with intimation of a likely prognosis and response to treatments. These classifications help to define homogeneous groups to optimise treatment and to determine prognosis with improved precision. In parallel, however, there is a need to incorporate a seizure classification system based on seizure semiology that infers the lateralisation and localisation of the networks underpinning seizures. This is particularly important if resection or focal therapies are considered.

A change of perspective is needed, with epileptic seizures being overtly regarded as a symptom complex. The related comorbidities, aetiologies and risk factors represent a range of conditions in which seizures can form a part. Commonalities with other paroxysmal disorders, such as migraine, are also important to recognise. The conceptualisation of epilepsy comorbidities as precipitating factors and seizures as the major symptom will improve understanding of epilepsy, and catalyse research and advances in clinical practice.[1]

In the past 20 years, understanding the pathophysiology of epileptogenesis and seizure onset, propagation and cessation has advanced, leading to new therapeutic targets and disease-modifying treatments. Focally delivered genetic therapies that reduce network excitability are anticipated to start clinical trials next year. This approach consists of a direct intracerebral injection of engineered potassium channel genes into epileptic foci in individuals who do not have known genetic conditions and who are candidates for resective surgery.[2,3] Other approaches include conditional activation of gene products, such as optogenetics or chemogenetics. In the latter, Designer Receptors Exclusively Activated by Designer Drugs are modified human proteins which are activated by an oral drug and not by endogenous ligands. For example, a mutated human muscarinic receptor that does not respond to endogenous acetylcholine, but is activated by exogenous agents.[4]

There have also been advances in epilepsy genetics, underpinned by multicentre collaborations defining large well-phenotyped cohorts, molecular genetics, and bio-informatics. Many pathogenic mutations have been identified since the first monogenetic disorder associated with epileptic seizures was found in 1995.

Among the most assessed pathogenic mutations are modifications of the sodium channel gene (*SCN1A*) causing a loss of function with various phenotypes, including febrile seizures, generalised epilepsy with febrile seizures plus, Dravet syndrome, intractable childhood epilepsy with generalised tonic-clonic seizures, myoclonic-astatic epilepsy, infantile spasms, focal epilepsies and vaccine-related encephalopathy. There is considerable genotype-phenotype heterogeneity and genetic pleiotropy, as with many other genetic disorders. The diagnosis of an *SCN1A* alteration can have implications for therapy—for instance, a risk of worsening with sodium channel blockers. Furthermore, characterising whether mutations cause a loss or gain of function will inform choices of

which conventional antiseizure medications to use and which to avoid. Tentative genetic treatments for Dravet syndrome include antisense oligonucleotides targeting an alternatively spliced exon that normally down-regulates the translation of the sodium channel.[5]

Focused gene sequencing, whole-exome sequencing, and genome-wide studies have detected many pathogenic mutations in people with epilepsy, particularly in those with epileptic encephalopathies and developmental delay.[6] There is not a single causative gene in most individuals with common epilepsies. Complex gene inheritances can act as positive or negative risk factors contributing to the likelihood of developing epilepsy after an acquired insult such as a head injury.

In presumed genetic generalised epilepsies, a genetic cause has been identified in a small proportion—eg, variants in *SCN1A*, *ICK*, *SLC2A1*, *GABRG2*, and an increased representation of epileptic encephalopathy genes, and with copy number variants noted in 3%.[7]

In focal epilepsies, mutations in GATOR1 protein genes (*NPRL2*, *NPRL3*, *DEPDC5*), part of the mTOR pathway, have an important role, as do *KCNT1* and *GRIN2A*. Somatic mutations in GATOR proteins might underlie focal cortical dysplasia and some focal epilepsies and can be expressed as mosaicisms.[8]

The PCDH19 disorder provides an example of the complex genetic architecture of seizure disorders. Due to complex interactions between random chromosome inactivation, potential somatic mosaicism, and abnormal cell interrelationships, the phenotype includes epilepsy, cognitive impairment, and autism in heterozygote females.

A fuller exposition of the interplay of genetic predispositions for epilepsies and the treatment implications are anticipated with the elucidation of the genetic architecture of the spectrum of paroxysmal disorders, including epilepsy, over the next 20 years.

Approaches to estimating the risk of developing epilepsy after stroke[9] and head trauma have become more sophisticated.[10] The role of inflammation and the blood-brain barrier in the causation of epilepsy has been examined but has not yet spawned disease-modifying therapies. There needs to be more emphasis on primary prevention: improved obstetric and paediatric care, reducing head injuries in industrial settings, road traffic accidents, avoiding wars, reducing strokes and eradication of parasites such as *Taenia Solium* and *Plasmodium Falciparum* with public health measures.

The promise of being able to predict seizures has not yet been realised, but there are now wearable devices that can detect convulsive seizures, enabling prompt attention by caregivers and thus reducing morbidity risk.[11]

Seizure suppressing medications are the current mainstay of epilepsy treatment. Lacosamide, brivaracetam and perampanel became available in the past 20 years. These medications have not, however, been a significant step forward, with only a few percent of those who have previously tried four or more medications becoming seizure-free for more than 12-months. Enter cenobamate, which appears to be more effective, with about a third of patients becoming seizure-free and a 12-month retention of 80%, which compares to retentions of about 60% for perampanel, lacosamide, and brivaracetam, and 72% for levetiracetam, at the same timepoint.[12]

Brain imaging for epilepsy has developed hugely over the past 20 years. The advent of 3T and then 7T MRI magnets, with improved gradients and acquisitions, have led to the identification of increasingly subtle cerebral abnormalities that can underlie focal epilepsies, particularly subtle malformations of brain development.[13] Post-acquisition

processing of MRI data and artificial intelligence techniques further increases sensitivity.[14] There is an inevitable balance that needs to be struck between sensitivity and specificity when applying the results to individuals in whom surgical treatment is being considered.[15]

At the other extreme from studies of individuals, extensive multicentre studies illuminate abnormalities of brain structure associated with epilepsy, with identifiable patterns of grey matter atrophy and white matter abnormalities in generalised and focal epilepsies and inferring abnormalities of networks.[16] Longitudinal studies are needed to determine whether changes are causes or consequences of epilepsy.

Epilepsies are now recognised as network disorders rather being solely due to a focal abnormality. Widespread abnormalities of structural and functional connectivity are now known to reduce the chances of seizure freedom after a focal resection. Going forward, the integration of multimodal methods to identify focal abnormalities and to determine if there are widespread abnormalities might improve individual selection for surgery.[17]

Epilepsy surgery has become established in more centres over the past 20 years, with an evolution of the case-mix. There has been a decline in hippocampal sclerosis, reflecting the treatment of many of those with hippocampal sclerosis in the prevalent population and the better treatment of early childhood convulsions. In parallel, there has been an increase in people considering epilepsy surgery who have extratemporal foci and in whom MRI scans do not show an evident abnormality, underlining the need for more sensitive brain imaging.[18]

Epilepsy surgery is becoming less invasive, with the aim to reduce the surgical footprint on the brain and to reduce adverse consequences of surgery, particularly on language, memory, and vision. 3D-multimodal image guidance offers precise resection planning, individualised to each person, to maximise the possibility of seizure control and minimise collateral damage.[19] Laser interstitial thermal therapy has gained acceptance by avoiding a craniotomy and ablating the epileptogenic zones with laser light.[20] Delivery of thermo-coagulating electric current through stereotactically placed intracerebral electrodes used to determine the sites of seizure spread and early spread might also be effective.

Other minimally invasive focal therapies include brain stimulation with responsive neurostimulators activated by the detection of EEG rhythms suggesting the likelihood of a seizure, and the possibilities of local drug delivery and focal genetic therapy. An intriguing concept is to sample DNA from explanted intracranial electrodes to identify epileptogenic somatic mosaic mutations that might lead to specific focal or systemic therapy. In another 20 years, we hope to be able to look back on craniotomies as being of only historical interest.

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