The concept of disease modification

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Abstract

Traditionally treatment of epileptic seizures has been symptomatic, namely medication has been targeted at raising the threshold to the occurrence of epileptic seizures. This has had little impact on the rate of drug resistance over time, or impact on comorbidities such as learning and behaviour particularly in the early onset epilepsies. The advent of advanced neuroimaging and genomics has revealed the cause of the epilepsy in a much higher percentage, and advanced our knowledge as to the underlying pathophysiology. This has given us the opportunity to turn to the possibility of interventional treatment, targeting the underlying cause, and consequently the possibility of changing the natural history of disease. Here we review the options open to us, and the evidence to date.

Introduction

Much of what we do in day to day clinical practice in childhood epilepsy is utilise treatment to attempt to prevent the occurrence of clinical seizures, namely symptomatic treatment. Over time we have become aware, that specifically in the early onset epilepsies, there is a negative evolution with poor neurodevelopmental progress, with ultimately learning disabilities and behavioural problems. In many, seizures continue despite anti-seizure medications. Often it is unclear as to the relative impact of the seizures, the ongoing epileptic activity, medication or underlying cause on the ultimate outcome. The issue remains as to whether more effective treatments will be available once the underlying cause is determined, and whether these more precision treatments can have any positive impact on the ultimate outcome, particularly when these are used earlier in the epileptogenic process.

Disease modification is defined as changes that may be influenced by treatments or interventions and that affect the underlying pathophysiology of the disease and have beneficial outcome on the clinical course. A traditional concept of epilepsy has been the notion of epileptogenesis – that there may be an initial epileptogenic trigger or injury, that there is a subsequent latent period with the further emergence of seizures and consequent chronic epilepsy at a later stage[1] . Following this model, true prevention and consequent disease modification would rely on recognition of the trigger and a modifying agent to the latent phase to prevent the development of seizures. However, in the developing brain there are many stages at which an 'insult' may have an impact, not least as the brain continues to develop through childhood and that 'insult' may take many different forms (for example genetic mutations, malformation of cortical malformation, prenatal brain infections).

Are we thinking about epilepsy in the right way?

Traditionally agents used to treat seizures have been discovered in the majority by accident through testing different compounds on animal and in vitro models. Subsequently their proposed mechanism (s) of action have been determined through further testing in the laboratory, with proposed inhibitory mechanisms at differing parts of the neurotransmitter junction. In this classic view of treatment, we are only targeting seizures.

However, seizures have to be seen as a symptom of many different causes. With significant advances in both neuroimaging and genomics, the cause of many early onset epilepsies can now be determined. In those with lesional epilepsies, specifically those with unilateral lesions, resective surgery may provide a real option of a cure from seizures, with wean of medication[2]. The

assumption is that in many of these children seizures are a major contribution to their learning and behaviour – an "epileptic encephalopathy", where the epilepsy and epileptic activity is contributing to the cognitive impairment over and above what would be considered from the underlying pathology alone. Certainly data suggest that longer term improvements may be seen, specifically related to both stopping seizures and weaning from antiepileptic medication[3,4].

However, in genetic epilepsies, there is a major contribution not only from the epilepsy but also the underlying genetic defect. For instance, in the Dravet syndrome we know that diminishing seizure frequency only has a limited effect on cognitive development[5]. With an understanding of the gene pathway that may be coded for by a specific mutation, maybe we can think of treatments that can be more targeted at the pathways rather than the seizures alone, and through this way forward, an impact be made on the overall outcome.

Disease modification – the options

1.Utilisation of optimised treatments

With an understanding of specifically sodium channelopathies, we have become aware that standard treatments may aggravate seizures and ultimately impact on outcome. A classic example of this is SCN1A related Dravet syndrome, where there is a possibility of aggravation of seizures by medications such as carbamazepine, lamotrigine and phenytoin[6]. A recent study evaluated the influence of contraindicated medication use on cognitive outcome, clearly showing that those where contraindicated medication was used for <11m in the first five years of life had a higher IQ than those where such medication was used over a longer period of time[7]. Re-evaluation of adults with SCN1A positive Dravet syndrome with a change in medication led to improvements in patients as old as 60 years[8]. However not all individuals may react adversely to such medication and therefore in older individuals one may need to be wary of withdrawal if they have been sustained on such medication for some time. There are reports of such individuals experiencing an exacerbation of seizures with later withdrawal of such medication[9]. Another example where early diagnosis may lead to more optimal treatment and improved cognitive outcomes is epilepsy associated with SLC2A1 mutations, GLUT1 transporter defects. Early diagnosis and utilisation of the ketogenic diet has been shown to result in improved cognitive outcomes[10].

2. Pre-emptive treatment of at risk individuals

Infantile spasms and related West syndrome is one condition thought to be a true epileptic encephalopathy. Often the children present with developmental plateau prior to presentation with the typical infantile spasms, related to the earlier development of the highly disorganised EEG, hypsarrhythmia. West syndrome maybe the result of many different aetiologies, some of which may be known about in advance. In one study, children with known hypoxic ischaemic injury at birth and considered to be at high risk of developing seizures were followed with recurrent EEG, and those likely to develop West syndrome reliably identified several weeks before the development of hypsarrhythmia; those treated early did not develop spasms or hypsarrhythmia but no clear impact on outcome could be determined with small numbers and duration of followup[11].

Tuberous sclerosis (TS) is a well-known cause of infantile spasms and West syndrome. In these children seizures occur in more than 80% of individuals, with 70% starting before the age of 12 month[12] . Further, intellectual disability is highly associated with the occurrence of seizures. In the

original Mayo series all those that did not have a history of seizures had normal cognitive outcome, whereas 69% those who presented with seizures had intellectual disability. The question arises as to whether children diagnosed with Tuberous Sclerosis at birth can be preventively treated, to avoid infantile spasms and improve developmental outcomes. A pilot study performed in Poland attempted to address this. In an open label study 45 infants diagnosed with TS at birth were divided into two groups, 31 to receive standard treatment (initiation of vigabatrin when clinical spasms or other seizures developed) and 14 preventative, monitored with EEG and initiated on vigabatrin when active multifocal discharges were seen. At 24 months' intellectual disability was significantly more frequent and severe in the standard compared to the preventative group, 48% vs 14%, p=0.031. The preventive group was also characterised by higher ratio of seizure free patients, lower incidence of drug resistant epilepsy and lower number of patients requiring polytherapy[13]. A subsequent EU funded multicentre study, EpiSTOP was initiated to answer the question more definitively with 100 TS children recruited. All infants were followed with regular EEGs and when focal discharges (for more than 10% of the time) or multifocal discharges occurred, children were randomized to a standard of care group or to preventive treatment group (vigabatrin>80mg/kg/day). Preliminary results do confirm that the onset of active epilepsy is later (on average 2 months) in the preventive group than in the standard group. In addition, no infant in the preventive group developed infantile spasms. The developmental outcome did not differ between the two groups however, but this might be due to the relatively short follow up to date (24 months). The study also showed that intellectual outcome is related to seizure frequency, whereas the development of autistic behaviour is not influenced significantly by this[14,15].

3. Targeting the gene pathway

Increasingly many epilepsies are being determined to be monogenic, most commonly the epilepsies with onset under one year. With an understanding of the gene mutation and coded pathway, we gain a better understanding of the pathophysiology, and are able to possibly target the underlying defect[16]. In part this can be seen in epilepsy associated with Tuberous Sclerosis, the result of TSC1 and/or TSC2 mutations. Although the epilepsy has traditionally thought to arise from the tubers, histologically indistinguishable from focal cortical dysplasia type IIb, there is animal evidence that that the mTOR pathway may also be relevant. A recent randomised controlled trial demonstrated efficacy of the mTOR inhibitor everolimus in epilepsy the result of tuberous sclerosis compared to placebo[17]. Tantalisingly, compared to placebo the higher and lower dose everolimus demonstrated increased efficacy over time, suggesting possible disease modification.

4. Replacement therapy

Ceroid Lipoid Neurofuscinosis (CLN) is a progressive myoclonic epilepsy for which in excess of 14 mutations have been determined. CLN2, the result of a mutation in the TPP1 gene, results in a deficiency of lysosomal serine peptidase. This results in accumulation of lysosomal storage material that causes degenerative changes in neurons throughout the central nervous system and retina. Patients may experience language delay but >50% appear developmentally normal until the age of 3 years. Natural history studies have shown steady subsequent deterioration from 24 to 96 months with the development of seizures, ataxia, language and motor loss, progressive dementia and early death. Standard of care has traditionally been supportive and palliative. Cerlionase alfa, a recombinant proenzyme form of human TPP1, is an enzyme-replacement therapy that has been

utilised in children with CLN2 disease. In a multicentre, open-label study, 24 children with CLN2 disease were enrolled in an open label study evaluating the effect of intraventricular infusion of cerliponase alfa every 2 weeks in children with CLN2 disease age between 3 and 16 years[18]. The median time until a 2 point decline in a motor language score was not reached for patients but was 345 days for historical controls. In those experiencing convulsive seizures improvement was seen. Treatment of the underlying cause in this progressive myoclonic epilepsy has been demonstrated to alter the natural history through disease modification.

5. Genetic therapy

With increased knowledge of specific gene defects as a cause of neurological disease, the possibility arises of targeted genetic therapy. This has been well illustrated in neuromuscular disease. Spinal Muscular Atrophy (SMA) is a neurodegenerative disease primarily characterized by a loss of spinal motor neurons, leading to progressive paralysis and premature death in the most severe cases. SMA is caused by homozygous deletion of the survival motor neuron 1 (SMN1) gene, leading to low levels of SMN protein. However, a second SMN gene (SMN2) exists, which can be therapeutically targeted to increase SMN levels. This has recently led to the first disease-modifying therapy for SMA gaining formal approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Nusinersen is a modified antisense oligonucleotide that targets the splicing of SMN2, leading to increased SMN protein levels and clinical improvement in some clinical phenotypes[19,20]. The question remains as to whether genetic modification may be a treatment option for genetic epilepsies. The possibility of genetic therapy in SCN1A related epilepsies is being evaluated.

Viral-vector-mediated gene transfer offers the opportunity to design a rational treatment that builds on mechanistic understanding of seizure generation and that can be targeted to specific neuronal populations in epileptogenic foci. Recent animal studies have demonstrated successful proof of principle using a viral plasmid bearing a fully codon-optimized sequence encoding a glutamate-gated Cl– channel, with the aim of inhibiting neurons in response to pathological accumulation of extracellular glutamate, a hallmark of excessive synchronous discharges of excitatory neurons in seizures[21]

Conclusion

Our management of the epilepsies has traditionally involved evaluation of the electroclinical phenotype and selection of optimised treatment from our range of antiepileptic medications. Seizure and neurodevelopmental outlook however has remained poor, specifically for the early onset epilepsies. An improved determination of underlying cause has led to better understanding of pathophysiology, and therefore a real possibility of interventional rather than symptomatic treatment. Such an approach may lead to improved outcomes in the longer term.

References

1.   Clossen BL, Samba Reddy, D. Novel therapeutic approaches for disease-modification of epileptogenisis for curing epilepsy. Biochimica et Biophysica Acta 2017;1803:1519-1538

2.   Braun K, Cross JH Pediatric epilepsy surgery: the earlier the better Expert Rev Neurother. 2018;18:261-263

3.   Skirrow C, Cross JH, Cormack F, et al Long-term outcome after temporal lobe surgery in childhood: intellectual gains are correlated with brain volume change. Neurology 2011;76:1330-1337

4.   Skirrow C, Cross JH, Owens R, et al Determinants of IQ outcome after focal epilepsy surgery in childhood: a longitudinal case-control neuroimaging study' Epilepsia 2019 May;60(5):872-884

5.   Nabbout R, Chemaly N, Chipaux M, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet Journal of Rare Diseases 2012;8:176-

6.   Guerrini R, Dravet C, Genton P, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy Epilepsia 1996;39:508-512

7.   de Lange IM, Gunning B, Sonsma ACM, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN1A-related seizure phenotypes. Epilepsia. 2018;59:1154-1165.

8.   Catarino CB, Liu JYW., Liagkouras I, et al Dravet Syndrome as epileptic encephalopathy: evidence from very long-term course and neuropathology Brain 2011;134(Pt 10):2982-3010

9.   Dalic L, Mullen SA, Roulet Perez E, et al. Lamotrigine can be beneficial in patients with Dravet Syndrome Dev Med Child Neurol 2015;57:200-2

10.   Ramm-Pettersen A, Nakken KO, Skogseid IM et al Good outcome in patients with early dietary treatment of GLUT-1 deficiency syndrome: results from a retrospective Norwegian study. Dev Med Child Neurol 2013; 55: 440-447

11.   Philippi H, Wohlrab G, Bettendorf U et al. Electroencephalographic evolution of hypsarrhythmia: toward an early treatment option Epilepsia 2008;49:1859-64

12.   Kingswood JC, d'Augères GB, Belousova E, et al TuberOus SClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. Orphanet J Rare Dis. 2017 Jan 5;12(1):2

13.   Jozwiak S, Kotulska K Domanska-Pakiela D et al Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paed Neurol, 2011;15:424-431

14. Moavero R, Benvenuto A, Emberti Gialloreti L, et al. Early Clinical Predictors of Autism Spectrum Disorder in Infants with Tuberous Sclerosis Complex: Results from the EPISTOP Study. J Clin Med. 2019 Jun 3;8(6).

15.   Jozwiak S, Aronica E, Curatolo P, et al, EPISTOP and EPIMARKER Abstract, IEC Meeting Bangkok 2019

16.   MacTague A, Howells KB, Cross JH, et al. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol; 2016;15:304-316

17.   French JA, Lawson JA, Yapici Z et al Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double blind, placebo-controlled study. Lancet 2016; 388: 2153–63.

18.   Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular Cerliponase Alfa for CLN2 disease. N Engl J Med 2018;278:1898-907.

19.   Finkel RS, Mercuri E, Darras BT et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Medl 2017;377:1723-1732

20.   Shorrock HK, Gillingwater TH, Groen EJN. Overview of current drugs and molecules in development for spinal muscular atrophy Drugs 2018;78:293-305

21.   Lieb A, Qui Y, Dixon CL et al Biochemical autoregulatory gene therapy for focal epilepsy. Nature Medicine 2018; 24: 1324–1329