New epilepsy treatment in children: upcoming strategies and rewind to ancient times and concepts

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Abstract

The epilepsies are the most common chronic neurological disorders in children. Considerable steps towards a better understanding of different aspects of the once considered 'sacred disease' have been made over the last two centuries, culminating in the development of new pharmacological and alternative antiepileptic treatments. However, principles of antiepileptic drug therapies have changed little since their breakthrough in the 20th century and the emphasis still lies on treating the symptom by enhancing inhibitory currents and suppressing excitatory networks rather than on addressing underlying neurobiological mechanisms. Around one third of the patients do not respond to the currently available drugs. New therapeutic strategies are on the horizon comprising inflammatory, immune and intracellular pathway targeting, as well as neuromodulation and novel surgical and dietary interventions. Furthermore, the prospect of personalized treatment for epilepsy using epigenetic and genetic techniques is becoming a reality. We discuss current and new concepts and future possibilities in the effort to cure the epilepsies.

Keywords antiepileptic treatment; autoimmune epilepsy; children; dietary treatment; epilepsy; epilepsy surgery; neuroinflammation; neurostimulation; personalized medicine

Clinical practice points

- Diagnosing and treating the epilepsies is important to lower the possible impact of recurrent seizures on cognition, behaviour and quality of live.
- Surgery is a valid option in the treatment of selected children with drug resistant focal epilepsy; a referral for assessment at one of four centres within the National Children's Epilepsy Surgery Service should be considered early.
- Dietary treatment may be an efficient alternative when drugs fail to achieve seizure-control and some specific electroclinical epilepsy syndromes may respond particularly well to this treatment.
- The immune system plays a crucial role for epilepsy generation and propagation and a better understanding of these neurobiological mechanisms may open for new treatment targets.

Introduction

Epilepsy is a chronic disease of the brain affecting 3.5–5/1000 children in the developed countries with 41–187/100,000 new cases every year. The enduring predisposition to generate seizures, the frequently associated neuropsychological and behavioural disorders and the social consequences of this disorder can significantly impact quality of life. A high burden of clinical seizures and frequent interictal epileptic discharges may have an adverse effect on the developing brain. Furthermore, children with epilepsy have an up to tenfold higher risk of dying compared to the general population. The primary cause of death in such patients is in the first place related to the underlying aetiology, but seizure-related accidents, refractory status epilepticus with fatal outcome and SUDEP (sudden unexplained death in epilepsy) also may occur. Vigorous attempts at complete seizure control is mandatory to substantially reduce the possible detrimental outcomes on cognition, behaviour and quality of life of these children.

This review discusses current and emerging concepts of antiepileptic treatment strategies. It also provides some insights into the recent advances that have been made and have resulted in a better understanding of the pathophysiological mechanisms underlying the epilepsies. These have identified potential targets for future antiepileptogenic and disease-modifying treatment.

Cutting and burning- curing epilepsy with surgery

Around one third of the children will not achieve appropriate seizure control with standard pharmacological treatment, the likelihood of becoming seizure free with any further medication being extremely low after trial of two appropriately selected AEDs. Carefully selected children with a drug-resistant epilepsy related or not to a visible lesion on the MRI may be suitable for epilepsy surgery. The number of candidate paediatric patients is constantly increasing, with advances in presurgical evaluation techniques aiming to determine seizure onset zones and networks including imaging and invasive EEG monitoring utilising subdural grids or stereoencephalography (sEEG).

Simply put, the goal of curative surgery is to remove the region which is generating the seizures (epileptogenic focus) without producing any further neurological deficit. This may be achieved by lesionectomy or wider resections including focal, lobar and multilobar (including hemispheric) removal which are used when the epileptogenic zone is more extensive. To interrupt seizure networks, lobes or even the entire hemisphere can be disconnected surgically from the normal functioning portions of the brain with good success in achieving seizure freedom or at least significant seizure reduction.

When there are multiple epileptogenic foci or an epileptogenic focus is not within a resectable area, thermocoagulation via the

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depth-electrodes may be used to ablate the onset zones or to cut through the pathological network. This type of surgery is often considered to be palliative rather than curative.

Surgery is a valid option in the treatment of selected children and an early intervention may lead also to improved long-term outcome of behaviour and cognition. It should therefore not be considered just as a last resort. All children with criteria including epilepsy thought to arise from a single lesion visible on MRI, or who have continuing focal seizures with or without visible lesion following a trial of two antiepileptic medications should be referred for assessment at one of four centres within the National Children's Epilepsy Surgery Service.

Wiring and reprogramming the brain

The first mention of neurostimulation dates back to the ancient Romans when the electric discharges of the torpedo-fish were used to alleviate pain. The rationale behind these techniques, when applied to epilepsy, is to interrupt or tune-down the pathological networks sparing the function of eloquent zones such as language or motor cortex. The electrical pulses are delivered to specific brain areas by stimulating either the peripheral or the central nervous system.

Neurostimulation has disease modifying effects as increasing efficacy of seizure-reduction is observed over the years of treatment. It is assumed that neuronal networks are reprogrammed progressively, and long-term potentiation or depression of synaptic strength are believed to play a major role in such changes in neuroplasticity. However, the underlying neurobiological mechanisms of the antiepileptic effects of neuromodulation are not fully understood and it remains a mystery why some patients respond and others do not.

Despite the longstanding interest in these palliative techniques, devices for clinical use are fairly recent and currently offered only to patients who are not suitable or have failed resective surgery. At present most information derives from the modest experience in adult patients, although these treatments are becoming increasingly available in the paediatric world.

Vagus nerve stimulation (VNS)

VNS is the most widely used neurostimulation technique in both adults and children. The electrodes are implanted around the cervical portion of the left vagus nerve and connected to a 'pacemaker' located under the skin in the pectoral area. The exact mechanism of seizure abortion and prevention is still unclear. A recent animal study showed that VNS not only has complex effects on the brain's regional activity, but it also affects interregional functional organisation. The positive effect on seizure suppression can take several months to manifest and it is now well-known that the overall efficacy increases over years. In patients with pharmacoresistant epilepsy, seizure reduction with VNS is reported to be equivalent to any new drug-attempt. However, considering that in most cases VNS is employed only as a last resort, higher success rates may be seen if it is offered sooner. Apart from the usually transient hoarseness of voice, coughing or throat discomfort, it is well-tolerated in children.

Deep brain stimulation (DBS)

Amongst the various explored targets for antiepileptic treatment via DBS, the thalamus, in particular the anterior nucleus, and the hypothalamus seem to be the most promising. They are both part of the Papez-circuit, which is implicated in emotion and memory functions and thought to play a central role in seizure propagation given its strategic location. RCTs in adults have yielded robust evidence regarding safety and efficacy of stimulation of these two structures. Open-loop and, more recently, also closed-loop systems are employed. In the former, the electrode is placed directly on the structure to stimulate, whereas the latter employ additional electrodes placed in various locations on the cortex to record seizures and consequently deliver stimuli to abort a nascent seizure. In children, DBS is a well-established technique for movement disorders. Although results to treat epilepsy appear to be encouraging, only a few paediatric cases are reported in the literature.

Cortical stimulation (CS)

CS was first used in the late 19th century to create the functional map of the brain. Only in 1999 Lesser et al observed a significant decrease of duration of epileptic discharges, when brief bursts of pulse stimulation were applied through subdural electrodes and CS has become a treatment option since. Two recent large multicentric prospective studies in adult patients with medically intractable focal epilepsy, showed responsive neuromodulation (RNS) to be a safe and effective. RNS is a closed-loop system where the neurostimulator senses electrographic activity through the depth or cortical strip-electrodes and in response delivers brief stimulation pulses with the intent to interrupt initiating seizures. There have been no RCTs for chronic cortical stimulation as yet. A group of the Mayo Clinic reported 13 adult cases efficiently treated with chronic subthreshold cortical stimulation. Recently, short periods ranging from 20 to 161 hours of chronic cortical stimulation were applied with success in five children who underwent invasive monitoring for presurgical evaluation. All but one showed a significant seizure reduction (>50%) during the treatment and interestingly, one patient became completely seizure free (follow-up 30 months). Steps forward with more prolonged cortical stimulation to lower the probability of seizure-recurrence are made only cautiously because of the concern of damaging the stimulated cortex and this is particularly true for the developing brain.

Non-invasive neuromodulation

Non-invasive neuromodulation techniques are under active investigation in the fields of neurology and psychiatry. Among these, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the most promising methods so far. Local cortical excitability is modulated by electrical currents, which in tDCS is conducted to the cortex via scalp electrodes, whereas in TMS it is induced by an electromagnetic coil applied to the scalp. Although data on efficacy and safety of tDCS are sparse and double-blind RCT studies are needed, it is a promising therapeutic tool for patients with chronic focal epilepsy. Single-pulse TMS is commonly used for evoked motor potentials in presurgical mapping of motor cortex. In therapeutic interventions for epilepsy, trains of TMS pulses (rTMS) are applied. Depending on the protocol rTMS is thought to induce long-term potentiation or depression of inhibitory and excitatory circuits respectively. In 2016 a Cochrane review concluded that it is safe and not associated with any adverse events, but evidence for

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