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REVIEW

Invasive Neuromodulation for the Treatment of Pediatric Epilepsy

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Abstract
Neuromodulatory strategies are increasingly adopted for the treatment of intractable epilepsy in children. These encompass a wide range of treatments aimed at externally stimulating neural circuitry in order to decrease seizure frequency. In the current review, the authors discuss the evidence for invasive neuromodulation, namely vagus nerve and deep brain stimulation in affected children. Putative mechanisms of action and biomarkers of treatment success are explored and evidence of the efficacy of invasive neuromodulation is highlighted.

Key Words Biomarkers · epilepsy · deep brain stimulation · seizures · vagus nerve stimulation

Introduction

Pediatric epilepsy is a debilitating condition with a prevalence of 3.2 to 5.5/1000 in North America and Europe [1, 2]. While seizure control may be achieved with medical therapy alone, approximately 30–35% of patients are ultimately diagnosed with drug-resistant epilepsy (DRE), defined by a failure to achieve seizure freedom despite two appropriately trialed anti-epileptic medications [3]. Alternative treatment modalities must therefore be considered including surgical resections, disconnections, or neuromodulatory techniques. Surgery may provide seizure freedom in appropriately selected candidates as demonstrated in a single-center trial showing freedom from seizure in 77% of patients who received surgery compared to 7% in the medical-therapy group [4]. Indeed, the Early Randomized Surgical Epilepsy Trial provided class I evidence for the benefit of early surgical resection compared to medical management in adolescents with temporal lobe epilepsy [5]. However, many children are not appropriate candidates for surgical resection particularly if there is no localization found on EEG or MRI, or if the seizure focus is centered in eloquent cortex. As such, neuromodulatory techniques have emerged as promising treatment options to reduce seizure burden for DRE.

Advancements in cortical mapping and neural network modeling have begun to shed light on the aberrant circuits implicated in epilepsy. This has helped pave the way for the application of various neuromodulatory techniques for the treatment of a variety of epileptic syndromes. Among these strategies, deep brain stimulation (DBS) and vagus nerve stimulation (VNS) have emerged as promising options for managing patients with DRE who may not be candidates for surgical treatment. A number of other neuromodulation strategies are also currently under investigation for their utility in DRE including the responsive neurostimulation system (RNS), pre-ablative cerebral warming, focused ultrasonography, and repetitive transcranial magnetic stimulation (rTMS). This review will focus on open stimulation systems, specifically the role of DBS and VNS for the treatment of DRE, briefly highlighting other neuromodulation systems, and will provide current evidence surrounding potential predictive markers to better inform patient selection.

Emerging Role of Neuromodulation in Epilepsy

Neuromodulatory strategies offer an adjunct treatment option for patients with DRE. These devices provide electrical or

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magnetic stimulation with the ultimate goal of reducing aberrant brain excitability which underlies seizure generation. Open-loop systems, such as DBS and most VNS devices, provide pre-programmed electrical stimulation to target specific brain structures thought to be implicated in seizures. Closed-loop systems provide stimulation in response to detection of seizure activity. Select RNS and VNS systems operate based on closed-loop principles. While treatment efficacy varies across studies, patient-related predictive factors are currently being studied in order to better determine ideal candidates for therapy.

Deep Brain Stimulation

Since its first application for the treatment of Parkinson's disease, DBS has expanded our armamentarium of treatment options for a variety of neurological disorders. Only recently has DBS been applied to the management of epilepsy with promising results.

Mechanism of Action

DBS delivers electrical stimulation to specific targets involved in seizure propagation in order to modulate cortical excitability, thereby reducing the frequency and severity of seizures. After the implantation of DBS electrodes, the stimulation can be adjusted to optimize therapeutic effects. The SANTE trial demonstrated significant reductions in monthly median seizure frequency from a multi-center prospective randomized cohort of 110 adults with DRE undergoing anterior nucleus DBS compared to controls [6]. In the pediatric population, DBS has been most successful with implantation into the centromedian thalamic nucleus with seizure frequency reduction of 30 to 100% in 17 of 18 patients [7–13]. There have been six pediatric patients who have benefitted from DBS placed bilaterally in the anterior thalamic nucleus (ATN) [10, 14–17]. In specific situations, DBS implanted into the hippocampus, subthalamic nucleus, posteromedial hypothalamus, and mammillothalamic tract has reduced seizure frequency.

The mechanism of DBS was initially hypothesized to simulate ablative procedures, because high-frequency stimulation brought on similar inhibitory treatment effects. However, high-frequency thalamic DBS has demonstrated both axonal activation within 2 mm of the electrode and subthreshold suppression [18]. After implantation in a specific target, changes in stimulation amplitude, frequency, and pulse width can affect the efficacy of treatment [19, 20]. EEG and fMRI data have demonstrated that DBS can provide more far-reaching effects and could modulate neural networks [21]. It is not yet clear how prolonged electrical stimulation will cause synaptic changes or neurochemical or receptor expression. In epilepsy, the cortical-striatal-thalamic network and the limbic circuit of Papez have been identified as important networks upon which neuromodulation can affect seizure propagation [21]. The hypothesis for the mechanism for ATN-DBS is the therapeutic modulation of ipsilateral Papez structures, including the entorhinal cortex, hippocampus, parahippocampal gyrus, mammillothalamic tract, and cingulate and inferior temporal gyrus [21–23].

Treatment Parameters

The current literature demonstrates that the stimulation parameters for CM electrodes in pediatric patients are usually characterized by lower frequencies (60–130 Hz), pulse width of 100 or 450 μs, and 6–8 V [9, 11, 12]. In patients who received ATN electrodes, stimulation parameters include frequencies ranging from 100 to 200 Hz, pulse width of 9–160 μs, and voltage of 1.5–8 V [14–17].

Predictors of Response

There is a paucity of data on predictors of response to DBS and studies that exist are limited by heterogeneous patient populations. DBS is rarely offered as the first-line treatment in epilepsy. Velasco et al. [11] have demonstrated seizure frequency improvement in 9 children with Lennox-Gastaut after the insertion of bilateral CM electrodes. DBS has also been considered in children who have already undergone resective surgery without significant post-operative seizure reduction [14, 24, 25]. DBS has been used in four children who had a history of status epilepticus with an improvement in seizure frequency in three of these children [15, 26].

Considerations in Children

Due to the dearth of long-term evidence of chronic brain stimulation in children, there is expected caution exercised prior to the use of DBS for epilepsy [27]. The youngest patient reported to undergo DBS for epilepsy was 4 years old [10], although it is unknown if there is a minimum age. With continued brain growth and development with age, it remains unknown whether electrode or wire migration may occur and compromise treatment effect or lead to complications. Children may also be more susceptible to infection from implanted foreign material. While literature pertaining to DBS in children is limited, there are four documented cases of children requiring permanent or temporary explantation of DBS electrodes due to infection or skin erosion [11, 24, 28].

Vagus Nerve Stimulation

VNS is considered a promising treatment strategy for DRE. While response rates remain variable, recent studies have

begun to uncover drivers of treatment effect and identify potential biomarkers to aid in patient selection.

Historical Context

The origins of our understanding of vagus nerve stimulation arise from pioneering neurophysiological studies that largely occurred in the first half of the twentieth century. Early work initially revealed that VNS can desynchronize cortical electrical activity in cats [29]. In 1952, Zanchetti et al. showed that VNS blocked interictal spiking in a cat model of epilepsy [30]. On the heels of these studies, further research revealed that VNS can reduce motor seizures and seizure frequency in various other animal models of epilepsy [31–33]. This body of pre-clinical work ultimately sets the stage for the first human implanted VNS device in 1988 [34].

Mechanism of Action

An integrated network of signals between brainstem centers and cortical structures is thought to underlie VNS treatment effect. Recently termed the "vagus afferent network" [35], this circuitry has been widely studied in an attempt to determine predictors of treatment response. Almost 80% of vagal fibers carry afferent sensory input. These signals are primarily sent to the nucleus tractus solitarius in the brainstem. From here, widespread projections are relayed to key brainstem centers including locus coeruleus, dorsal raphe nucleus, and parabrachial nucleus which then project diffusely to higher cortical structures.

With the application of molecular probing, immunohistochemical staining, and advanced functional imaging, a number of hypotheses have been generated regarding the underlying mechanism of action of VNS. Increased neuronal activity has been seen with VNS stimulation in nucleus tractus solitarius and its downstream targets [36]. Specifically, VNS increases neuronal signaling in brainstem centers such as locus coeruleus resulting in increased noradrenergic signaling within the amygdala, hippocampus, and prefrontal cortex which has been associated with improved treatment response. [37–41]

Modulation of thalamocortical connections is believed to be a key component of VNS effect. Changes in thalamic blood flow have been seen in patients receiving VNS [42], and increased activation within the thalamus is associated with improved treatment response [43]. Chronic VNS is also known to increase thalamocortical somatosensory evoked potential latency [44], and thalamic-anterior cingulate/insular cortex connections have been found to be enhanced in VNS responders [45]. There is strong evidence to suggest that VNS also induces plasticity within limbic system circuitry [46]. One hypothesis that has emerged posits that VNS leads to increased production of neurotrophic factors within limbic structures [39], enhancing neurogenesis which may facilitate the formation of new synapses to rewire aberrant circuitry [47]. VNS may also directly alter seizure frequency by way of decreasing seizure thresholds in amygdala and hippocampal neurons [48] [49, 50].

Increasing lines of evidence have implicated immunomodulation via hypothalamic signals as another mechanism of VNS treatment effect. Pro-inflammatory cytokines have been shown to promote seizure generation. Indeed, chronic VNS leads to decreases in pro-inflammatory cytokines such as IL-8 [51], and increased levels of anti-inflammatory cytokines have been found in VNS responders [52].

Treatment Parameters

VNS devices are often programmed two weeks after implantation. Both output current and duty cycle may be optimized in order to achieve treatment effect. Standard settings typically start at a current of 0.25 mA, frequency of 20–30 Hz, and pulse width of 250–500 μs. However, higher stimulation settings have been shown to increase seizure reduction rates and may thus be required in patients who do not initially respond to therapy. Indeed, Bunch et al. found that 20% of initial non-responders had improved response rates when higher stimulation parameters were employed [53]. Duty time indicates the time that stimulation is "on" or "off." Overall, settings of 30 s on and 5 min off have led to good treatment effect. However, some initial non-responders may show enhanced response with reductions in off time ≤ 1.1 min [54].

Predictors of Response

A growing body of work has helped identify potential predictors of VNS effect. Assessment of functional connections and electrical potentials has emerged as an appealing non-invasive approach to examine treatment response. For example, enhanced connectivity between the thalamus, anterior cingulate, and insular cortices has been shown to be associated with enhanced VNS treatment effect [45]. Moreover, patient scalp recording studies have shown that the P3 component of event-related potentials was associated with VNS responsiveness [55].

Whether certain seizure types may respond better to VNS remains unclear. In a small cohort of patients undergoing VNS for epilepsy, individuals with temporal seizure onset responded best to VNS relative to patients with other seizure foci [56]. The evidence is conflicting for the benefits of VNS on generalized or focal epileptiform discharges with some citing each type as having improved response [57, 58].

Considerations in Children

The majority of studies on VNS for DRE have focused on adult patients. While some reports have suggested that younger patients have better outcomes with VNS, the evidence is scarce and limited to small studies [59]. Nevertheless, evidence is growing for the safety and efficacy of VNS in the pediatric population. Treatment response has been reported to be quite good across studies with one cohort study reporting a mean reduction in seizure frequency of 71% by 36 months [60]. The side effect of VNS within this population is similarly understudied; however, to date, few adverse effects have been reported. [61–65]

Other Neuromodulatory Techniques

While DBS and VNS have gained the most attention as neuromodulatory adjuncts to treat DRE, a number of other strategies are currently being investigated. Responsive neurostimulation device (RNS) is the only system to date which continually monitors patient brain activity and subsequently responds to early seizure signals by delivering an electrical pulse to halt the generation of seizures. A randomized trial including 191 patients with DRE showed an almost twofold increase in the reduction of seizures among patients with RNS compared to controls [66].

Repetitive transcranial magnetic stimulation (rTMS) has most notably been investigated for the treatment of depression and other neuropsychiatric disorders. However, increasing evidence has demonstrated its potential utility in treating DRE in some patients. Low-frequency rTMS (0.33–1 Hz) has been effective at reducing seizure frequency in adults [67]. However, to date, no studies have examined the safety and utility of this therapy in children with DRE.

Conclusions

With the advent of more precise tools to measure, record, and modulate brain activity, neuromodulation systems hold the potential to treat neurological conditions previously deemed refractory to standard treatment modalities. The study of these devices has helped better understand the neural circuitry involved in epilepsy and identify potential predictive biomarkers of treatment response.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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