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Review Article

Vagus Nerve Stimulation for the Treatment of Epileptic Encephalopathy in Children

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ABSTRACT

Epilepsy is a neurological disease characterized by recurrent seizures of consciousness, convulsions, perceptual disorders, and parenthesis. Epileptic Encephalopathy (EE) is a serious cognitive and behavioral disorder caused by epileptic seizure beyond the underlying cause. The typical triad of EE includes frequent and drug resistant seizures, distinctive abnormal EEG changes and cognitive and behavioral retardation. Vagus Nerve Stimulation (VNS) is an antiepileptic method that modulates electrical activity in the brain by electrically stimulating the vagus nerve and projecting circuits to afferent fibers. VNS has been approved for the treatment of epilepsy in patients over 12 years of age since 1997. The indications are gradually extended to children, which provide a new approach for the treatment of EE children. This article reviews the application of VNS in children with epileptic encephalopathy from the aspects of effectively reducing seizures, improving cognitive development to a certain extent, treating comorbidities and improving the quality of family life.

Keywords: Epileptic encephalopathy; Vagus nerve stimulation; Pediatric neurosurgery

INTRODUCTION

Epilepsy is a central nervous system disease caused by highly synchronized abnormal discharge of brain neurons, which has repetitive, paroxysmal and stereotyped clinical seizures. Children are the peak age group of epilepsy. The prevalence of epilepsy in children aged 0-15 is about 3.9%-4.3% [1-3] and about 30% of patients still have more than four seizures per month after treatment with two antiepileptic drugs (immunotherapy or combination), which is called Drug Resistant Epilepsy (DRE) [4].

In 2010, The International League against Epilepsy (ILAE) defined Epileptic Encephalopathy (EE) as a serious cognitive and behavioral disorder caused by epileptic activity. These cognitive and behavioral disorders are beyond pathological expectation and may worsen over time [5]. The typical triad of epileptic encephalopathy is frequent and drug-resistant seizures, epileptiform discharges on the EEG, and cognitive behavioral retardation [6]. Most epileptic encephalopathy's begin in infancy or childhood and can be classified as age dependent epileptic encephalopathy, early infantile epileptic encephalopathy, infantile epileptic cerebropathy, and other age stage epileptic cerebropathy. In recent years, the concept of epileptic encephalopathy has been used to define multiple syndromes, including: Ohtahara syndrome, infantile spasms (West syndrome), dravet syndrome, lennox-gastaut syndrome, etc [7,8]. EE has the characteristics of young onset age, complex seizure form, high seizure frequency, serious cognitive impairment, low drug treatment efficiency and poor prognosis, which has become a hot and difficult point in global research. Early diagnosis and treatment is the key to control seizures, promote cognitive development and improve the quality of life of children with epilepsy. Vagus Nerve Stimulation (VNS) is a neuromodulator therapy in the surgical treatment of epilepsy, which plays an anti-epileptic effect by stimulating the Vagus nerve to activate the fibers projected upward to the nucleus tractus solitarii and further to the brainstem nuclei and cerebral cortex. More than 130,000 patients worldwide have been implanted with Vagus nerve stimulation devices. Compared with traditional epilepsy craniotomy, VNS has the advantages of small trauma, reversible operation and adjustable treatment parameters. This article

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mainly reviews the research progress on the efficacy of VNS in the treatment of children with epileptic encephalopathy.

LITERATURE REVIEW

VNS reduces seizures in children with epileptic encephalopathy

At present, the evaluation of the efficacy of VNS in the treatment of children with epilepsy is mainly based on the classification criteria proposed by in 2007. The reduction of seizure frequency and the improvement of seizure severity were evaluated comprehensively, and the view that the treatment was effective if the seizure frequency was reduced by ≥ 50% was accepted by most researchers [9]. Conducted a continuous follow-up study of 347 children with drug-resistant epilepsy aged 18 years and younger, with a mean age of 11.1 years, of whom 55.6% (86 cases) were younger than 12 years. Seizure frequency was reduced by ≥ 50% in 32.5%, 37.6%, and 43.8% of patients at 6, 12, and 24 months, respectively ($p<0.0001$) [10]. There are also several related studies [11-14]. Similar results have been reported, with an overall response rate of 53.0%-62.5%. Common conclusions include that VNS can effectively reduce the severity of seizures in children (shorter seizure duration, lighter seizure symptoms), and the response rate will gradually increase with the extension of treatment time. For EE patients, several studies have shown that VNS is effective in reducing seizures. Lennox-Gastaut syndrome is one of the early cases of EE that can be effectively treated by VNS. Level III evidence provided by the American academy of neurology in the VNS epilepsy evidence-based guidelines indicates that approximately 55% of patients with lennox-gastaut syndrome have a ≥ 50% reduction in seizure frequency after VNS [15]. Found that patients with lennox-gastaut syndrome in children with epilepsy had a significantly higher response rate to VNS than overall. A meta-analysis of 13 studies and 68 patients with dravet syndrome showed that 55.9% of patients with dravet syndrome had a ≥ 50% reduction in seizures after VNS treatment, with an average reduction of 55 percent [16]. Fang Tie et al. used VNS to treat 13 patients with west syndrome. The reduction rate of postoperative seizures increased significantly with the prolongation of treatment time. The average reduction rate of seizures in 6, 9 and 12 months was 52.86%, 71.67% and 83.33%, respectively [17]. Reported that in 6 of 7 patients with drug-resistant rett syndrome, the frequency of seizures was reduced by ≥ 50% after 12 months of VNS treatment, and the patients tolerated it well without complications [18]. In addition, children with epileptic encephalopathy are more likely to have severe status epilepticus, and it has been reported that VNS successfully treated a 13 years old patient with refractory generalized status epilepticus [19]. Similar studies have shown that VNS can stop seizures earlier in children with status epilepticus, thus effectively shortening the length of intensive care unit hospitalization and improving the prognosis [20]. Corpus Callostomy (CC) is a classic palliative procedure for the control of intractable seizures, which has been widely used for decades. An array of investigators compared the efficacy of CC and VNS in the treatment of epileptic encephalopathy by systematic review and meta-analysis [20]. The common conclusion is that CC is superior to VNS in the control of atonic seizures, while there is no significant difference in other seizure types, but VNS is safer than CC, and the complications related to VNS are relatively mild, reversible and easy to treat. Some scholars have also pointed out that both CC and VNS can be used as a second operation to reduce the seizure frequency when the other party's seizure control is not ideal. In general, although most studies have proved that VNS can improve seizures in children, most of them are retrospective analyses, and the number is less than that of similar studies on adults, which may have some bias. Therefore, the conclusions remain to be further confirmed by large sample randomized clinical trials.

VNS improves cognitive development in children with epileptic encephalopathy

Children are at a critical stage of intellectual development, and both seizures and antiepileptic drugs may adversely affect children's cognitive development. In fact, about 1/3 of children with epilepsy will have cognitive and/or behavioral disorders, and seizures in these children are often more difficult to control. In recent years, more and more researchers have begun to pay attention to how to improve the cognitive development of children with epilepsy. The specific mechanism of VNS in improving children's cognition is not completely clear. On the one hand, VNS, like CC, is a palliative surgery that can effectively reduce the number of seizures and antiepileptic drug dose to improve children's cognitive function. On the other hand, more and more studies have confirmed that VNS has a direct effect on cognition and emotion. Early animal experiments showed that short-term stimulation of the vagus nerve could improve the memory function of rats, and the effect was related to the stimulation intensity in a shape, and the effect was most obvious when the stimulation current was 0.4 mA. Compared VNS with sham stimulation and proposed that short-term VNS could improve the image memory function of epileptic patients. Unlike short-term studies, the effects of long-term VNS stimulation on cognition may be difficult to judge due to multiple factors such as child growth and development, drugs, and disease progression. Several studies support that long-term VNS stimulation can improve many advanced cognitive functions in children with epilepsy, including memory, language function, attention and social ability. VNS may also improve cognitive development in children with drug-resistant epileptic syndromes: 7 of 13 studies of VNS in Dravet syndrome have reported improvements in cognitive function. Compared the five cognitive indexes of 16 children with lennox-gastaut syndrome treated by VNS at 6 months after operation and before operation. The results showed that there was no deterioration in any of the five indicators, while there was improvement in mental age, attention and cognitive style. It is important to note that differences in quantitative measures of cognitive improvement before and after VNS are not always statistically significant. "The overall cognitive level of children after VNS is relatively stable and some cognitive functions may be improved" is the current consensus of the academic community.

VNS treatment of comorbidity in children with epileptic encephalopathy

Meta-analysis showed that about 50% of patients with epilepsy had more than one disease, and drug-resistant EE was more likely to have comorbidity. Among them, psychiatric comorbidities, including attention deficit, mental retardation, autism spectrum disorders and depressive disorders, account for about 50% of the total comorbidities. Autism Spectrum Disorders (ASD) has the most serious impact on children's mental development. Depressive disorders have a high recurrence rate in adolescents and can lead to self-harm and even suicide. Both of them have become the focus of research on comorbidity of epilepsy in children, and researchers have been looking for effective treatments for these diseases. Depression is a mood disorder characterized by significant and persistent low mood. Severe depressive disorders are characterized by pessimism and world-weariness, and may lead to self-mutilation and suicide. The drug of choice for the treatment of depression is a serotonin reuptake inhibitor, which can be used alone or in combination with psychotherapy. Treatment-Resistant Depression (TRD) can be diagnosed in children or adolescents who do not respond after 6 to 12 weeks of treatment, after excluding other factors have shown that the association between comorbidity of epilepsy and depression is based on an abnormal decrease in brain glucose metabolism and changes in functional metabolic networks. Initially, two large clinical trials in the last century confirmed that VNS was effective in reducing seizures and improving depressive symptoms in patients with refractory epilepsy. Since then, more and more studies have confirmed the effectiveness of VNS in patients with treatment resistant depression, and a recent literature review has shown that about 2/3 of TRD patients have improved symptoms after VNS treatment. Several studies have shown that VNS can improve brain energy metabolism, regulate the concentration of neurotransmitters and change the function of emotion related brain areas to treat depression. After Food and Drug Administration (FDA) approved VNS for the treatment of treatment resistant depression in 2005, some countries have gradually expanded the indications of VNS. Autism is a brain developmental disease characterized by the "two core" symptoms of verbal communication problems and repetitive stereotyped behaviors. Autism has a continuous spectrum of severity, called autism spectrum disorders. The prevalence of autism in the population can reach 1%-2%, and the morbidity has been on the rise in recent years. At present, there is a lack of effective treatment methods to improve the core symptoms of autism, which makes the families and society of autistic children face a heavy burden. Several laboratory studies have shown that autonomic dysfunction, cortical excitatory/inhibitory imbalance and abnormal functional connectivity of cognitive brain regions play an important role in the development of epilepsy and autism. Some studies have pointed out that drug resistant EE and ASD have a closer relationship, and CACNA1A gene mutation may be the common pathogenic gene of both. The theoretical basis of VNS for autism is that the abnormal decrease of vagus nerve tone is related to the behavioral and language disorders of autistic children, while the increase of vagus nerve tone may reduce the symptoms of communication disorders. Clinical studies have found that the symptoms of autism in children with epilepsy are also improved after VNS treatment. found that after 12 months of VNS treatment, the proportion of epileptic children with autism who had a ≥ 50% reduction in seizures was higher than that in the group without autism (62% *vs.* 56%), and the two groups of children had improved quality of life indicators such as language, memory and reaction, and the autistic group had a greater improvement in mood. In an earlier subgroup study of Landau-Kleffner syndrome with ASD, researchers found that seizures and quality of life improved in both groups after VNS and the improvement was more pronounced in the ASD group reported that 7 children with Rett syndrome had improved alertness after 12 months of VNS. However, there are few reports that VNS improves the core symptoms of ASD, and the limitation of studies on children with epilepsy and ASD lies in the lack of a unified assessment of the core symptoms of ASD. However, with the in-depth study of the pathogenesis of autism and the accumulation of experience in the treatment of mental and behavioral disorders with VNS, VNS is still hopeful to become a feasible way to treat epileptic comorbidities such as ASD.

VNS improves the quality of family life in children with epileptic encephalopathy

Although the evaluation methods of Quality of Life (QOL) in children with drug-resistant epilepsy are not completely consistent among researchers in different countries, they basically include seizure conditions (frequency, severity, duration, etc.), concentration, language, memory, learning, diet and sleep. The meta-analysis suggested that VNS treatment may have a positive impact on these aspects, especially for children with more psychosocial needs. Found that 70% of children had improved QoL after 12 months of VNS treatment, and 41.5% of children had greatly improved QoL after 24 months of VNS treatment. Pointed out that children with VNS implanted early (≤ 5 years) had better QoL improvement than those with VNS implanted later (>5 years). Sudden Unexpected Death in Epilepsy (SUDEP) is defined as the unexpected sudden death of a patient with epilepsy in the absence of a known structural cause of death. In a systematic review of guidelines from the American academy of neurology, SUDEP was associated with an increased frequency of Generalized Tonic Clonic Seizures (GTCS) in children with epilepsy at a rate of about 0.22 per 1000 patient. In a cohort study of more than 40,000 patients, 632 patients developed SUDEP, and the study showed that SUDEP decreased with the extension of follow-up time, which the researchers believe may be related to VNS treatment. Another large cohort study of the same type also supported this conclusion. In addition, epilepsy will bring a heavy financial burden to the families of patients, and the advantages of VNS in health economics have gradually been taken seriously. The study showed that VNS could save medical expenditure by reducing the use of antiepileptic drugs, the number of outpatient and emergency visits (80% of patients) and the number and length of hospitalization (67% of patients), and the cost savings would increase with the increase of treatment time. Some researchers have pointed out that after 1.5 years of continuous treatment of

VNS, the savings will exceed the cost of equipment and surgery, resulting in net cost savings and reducing the financial burden of families. Showed a significant decrease in the stress index of parents of children who received VNS for 12 months. To sum up, VNS may have some advantages in improving the QoL of children and families with refractory epilepsy, but the subjective factors in the QoL assessment process should not be ignored.

DISCUSSION

Limitations of VNS in the treatment of epileptic encephalopathy

Most researchers note the multiple advantages of VNS over other treatments, but everything should be viewed dialectically. Although VNS may reduce family medical expenditure in the long run, due to the high price of implantation surgery and equipment, the medical expenditure of VNS treatment will be very concentrated. The relatively high medical cost of implantation surgery makes it difficult for some families in developing countries to afford, and the guardians of children may have high expectations for the effect of this therapy. The reality is that for a considerable period of time after VNS implantation, the dosage of antiepileptic drugs in children cannot be reduced, and the frequency and severity of seizures are not significantly reduced. In addition, contrary to the expectation of some families that seizures should be eliminated quickly, the possibility of achieving complete seizure freedom through VNS treatment is relatively low (4-10%). All these may lead to the decline of the compliance of children and guardians to neuromodulation and drug treatment, and affect the long-term treatment effect. On the other hand, VNS treatment is not once and for all. In theory, the power supply life of VNS device is about ten years. If the child still needs to continue VNS treatment, changing the power supply of VNS device and even the whole device will expose the child to new risks. Their families also need to pay a large amount of medical expenses. Obviously, a long follow-up time is needed to assess the risk and cost of device replacement. At present, there are few studies with a follow-up time of up to ten years, so the research in this area needs to be paid attention to and strengthened. Other limitations include the inability to treat patients with shortwave and microwave diathermy after implantation of a stimulation pulse generator. Similarly, radiation therapy, external defibrillation, extracorporeal shock wave lithotripsy, or electro surgery is prohibited because they may damage the pulse generator. Patients with epileptic encephalopathy can be examined by 1.5 Tesla (T) MRI after VNS. However, it is necessary to adjust the output current of the pulse generator to 0 or shut down completely before the examination. After the MRI examination, it is necessary to retest the pulse generator and program it back to the original parameters. The significance of VNS treatment is not to eliminate seizures immediately, but an adjuvant and palliative therapy after considering the risks and benefits. Especially for children with epileptic encephalopathy whose brain function is severely impaired, VNS is not a panacea, but it may benefit children in multiple dimensions.

CONCLUSION

Since the discovery of epileptic encephalopathy, it has become a key and difficult clinical problem because of its great impact on the development of children, drug refractory, poor prognosis and other characteristics. VNS, as the most commonly used neuromodulation therapy for the treatment of epilepsy, has created a new era of modern neuromodulation therapy. Dozens of studies have demonstrated the effectiveness of VNS in the treatment of multiple types of epilepsy and epileptic syndromes, as well as tangible improvements in the quality of life of patients, providing clinicians with new options in the face of difficult epileptic encephalopathy.

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