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Young children with multidrug-resistant epilepsy and vagus nerve stimulation responding to perampanel: A case report

Yang H *et al*. Young child responding to perampanel

Abstract

BACKGROUND

Perampanel (PER), a third-generation antiepileptic drugs, is a selective and non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, and has been approved for the treatment of adults and adolescents with focal epilepsy. However, there are only a few studies about the efficacy and tolerability of PER in young children with multidrug-resistant epilepsy. In this case, we aimed to share our clinical experience in this group.

CASE SUMMARY

A four-year-old boy without perinatal asphyxia and familial history of epilepsy began to have ictal seizures since 14 mo old, with jerky movement of four limbs and head nodding. Abnormal multifocal discharge and background activity were recorded through electroencephalogram, and no pathogenic mutation was found in the whole exome sequencing for the patient and his parents. He had received valproate, levetiracetam, topiramate, oxcarbazepine, clonazepam and lacosamide sequentially at different times, but he still had frequent seizures even after vagus nerve stimulation (VNS) implantation. So he was diagnosed with idiopathic multidrug-resistant epilepsy. However, his seizure frequency was significantly reduced after PER administration in a dose-dependent manner, and the better cognitive behavior was observed. In addition, the adverse reactions of anger and aggression also appeared.

CONCLUSION

PER is effective as add-on therapy for young children with multidrug-resistant epilepsy who have previously undergone VNS implantation.

Key Words: Perampanel; Young children; Drug-resistant epilepsy; Vagus nerve stimulation; Case report

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Core Tip: Here, we reported a 4-year-old boy with multidrug-resistant epilepsy who still had frequent seizures after vagus nerve stimulation (VNS) implantation, and he showed significant response to perampanel (PER) as add-on in a dose-dependent manner. Considering its favorable cognitive profile and the similar efficacy and safety profile of PER in children under 12 years old as in older people, we proposed that the use of PER as add-on could further reduce the seizure frequency for young children with drug-resistant epilepsy and even after VNS implantation, which may be attributed to its novel antiepileptic mechanism.

INTRODUCTION

Of children with epilepsy, about 10% of them have drug-resistant epilepsy[1]. The treatment of drug-resistant epilepsy could be quite challenging, including resective surgery, ketogenic diet, vagus nerve stimulation (VNS), and new antiepileptic drugs (AEDs). The anticonvulsant perampanel (PER), a selective and non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, is a newly developed third-generation AED, possessing the completely different antiepileptic mechanisms with previous AEDs. Currently, PER is recommended by the American Academy of Neurology guideline as add-on therapy in treatment-resistant adult focal epilepsy to reduce epilepsy frequency (level A)[2]. However, there are only few studies reporting on the efficacy and safety of PER in children younger than 12 years old with drug-resistant epilepsy, especially in young children. In this paper, we presented a 4-year-old child with multidrug-resistant epilepsy in whom the seizures were not well controlled after VNS implantation, and PER administration significantly reduced seizure frequency in a dose-dependent manner. We aimed to describe our experience about reducing the seizures in multidrug-resistant young children with PER.

CASE PRESENTATION

Chief complaints

A 19-mo-old male young child presented with ictal seizures since 14 mo old, and was brought to our pediatric neurology department because of gradually increased seizure attack.

History of present illness

The history taken from the parents revealed that the patient began to have ictal seizures since 14 mo old, with jerky movement of four limbs and head nodding, and he experienced one seizure per week lasting for one to two seconds. His seizure frequency increased gradually, and when he was admitted to our department, he was experiencing up to 10-15 seizures per day lasting for 1-3 min each time, with hand raising and a series of head nodding. The patient could speak only simple words, and could not communicate with others and understand instructions.

History of past illness

The patient had a free previous medical history.

Personal and family history

His parents reported that there was no consanguinity, and the patient was born at full term *via* vaginal delivery with a birth weight of 3100 g. He had no perinatal asphyxia, and his Apgar scores were 10, 10, 10 at 1, 5 and 10 min of life, respectively. And he had no family history of epilepsy and other familial diseases.

Physical examination

Physical examination showed that the patient had normal consciousness but could not communicate with others and understand instructions. He showed normal appearance, and there was no abnormal skin mass or depigmentation. The muscle tension, strength and mobility of the limbs were normal.

Laboratory examinations

His laboratory examinations have nothing notable.

Imaging examinations

The cranial fluid-attenuated inversion recovery images showed patchy high-signal areas in the posterior part of bilateral lateral ventricle, and in the subcortical white matter of left occipital and temporal lobes (Figure 1).

FURTHER DIAGNOSTIC WORK-UP

The video-electroencephalography (vEEG) recordings showed irregular and slow background activity, as well as multifocal generalized sharp and (multi-) spike wave discharge (Figure 2A). And the high-amplitude slow waves with high-frequency discharges were recorded in vEEG during a seizure (Figure 2B). To determine the underlying cause of epilepsy, we performed whole exome sequencing for the patient and his parents, however, no pathogenic mutation was found.

FINAL DIAGNOSIS

This patient had both focal and generalized seizures, and was later diagnosed as idiopathic multidrug-resistant epilepsy.

TREATMENT

Several AEDs were applied to this patient sequentially. Valproate sodium (VPA, maximum dose 50 mg/kg/d) was started at 19 mo old after hospitalization, however it was ineffective on reducing seizure frequency. Such that levetiracetam (LEV, maximum dose 50 mg/kg/d) was add one month later, and the seizures were reduced by 60% after the add-on of LEV. When he was 32 and 33 mo old, topiramate (TPM, maximum dose 5 mg/kg/d) and oxcarbazepine (OXC, maximum dose 60 mg/kg/d) were added, respectively, and the seizure frequency was decreased gradually to 5-6 times per day.

VPA was replaced with clonazepam (CLZ, maximum dose 0.1 mg/kg/d) at 3 years old, however CLZ was discontinued after 3 mo due to ineffectiveness.

To further decrease seizure frequency, left VNS implantation was performed at 39 mo old for him, of whom the seizures were reduced by 50% to 2 seizures per day, and he became responsive to calling. The treatment of LEV, TPM and OXC was continued for 7 mo after the insertion of VNS, and OXC was gradually replaced with lacosamide (LCM, maximum dose 125 mg/d) in 3 mo for no improvement of seizure frequency. However, the seizures were still 2 times per day and LCM was discontinued. For this patient PER was started in his 4 years and 3 mo old at the initial dose of 2 mg/d (0.1 mg/kg/d, body weight 20 kg), and the seizures were significantly reduced to one time per 1-2 d. Three months later his PER was up-titrated to 4 mg/d (0.2 mg/kg/d) and his seizure frequency was one seizure per 2-3 d. And after two months his PER was added to current dose of 6 mg/d (0.3 mg/kg/d), which improved his seizure frequency to one seizure per 3-4 d lasting for 1-2 min each time (Figure 3).

OUTCOME AND FOLLOW-UP

At the last follow-up visit, seven months after the add-on of PER, the follow-up vEEG showed decrease in the frequency of multifocal discharges, and no seizure was observed during the monitoring (Figure 2C). Therefore, the improvements after the use of PER were both clinical and electrophysiological. Now the patient was responsive to calling, and could communicate with others and follow simple instructions, showing improved cognitive skills and language according to our observation and his parents' records. In addition, the adverse reactions of anger and aggressive behavior were noticed after the use of PER. Although the seizure-free status was not achieved in this patient after the 7-mo treatment of PER, he was currently in a close follow-up for long term effect of PER oral treatment.

DISCUSSION

PER is the first AED targeting AMPA receptor, which was approved by the United States Food and Drug Administration (FDA) for use to treat partial-onset seizures with or without secondarily generalized seizures for adult patients with epilepsy in September 2018[2,3]. Its great cognitive profile, ease of use of the titration scheme and the once-daily oral regimen give it advantages over other AEDs. Although the United States FDA approved the use of PER in persons ≥ 4 years of age according to the strategy that allows extrapolation of efficacy across populations[2], the reports about the efficacy and safety of PER in children under 12 years old with drug-resistant epilepsy are still limited. In this case, after the sequential use of six AEDs and the left VNS implantation, the 4-year-old patient still had frequent seizure attacks, while seizures were significantly reduced by more than 80% after adding PER in a dose-dependent manner. Hence, we believe that PER may be an effective and important add-on drug for treatment of multidrug-resistant epilepsy, especially in young children, which may be attributed to the novel antiepileptic mechanism of PER.

PER is a selective, noncompetitive antagonist of ionotropic AMPA glutamate receptor (AMPAR) that mediates the fast excitatory synaptic neurotransmission in the central nervous system (CNS). The AMPARs are expressed throughout the CNS, and are tetrameric complexes of four different types of subunits, including GluA1, GluA2, GluA3, and GluA4. The AMPAR subunits bind in pairs to form a variety of symmetric dimers, which next form functional ionic glutamate receptors surrounding a permeable cation channel of sodium (Na^+), potassium (K^+), and calcium(Ca^{2+}). Following the binding of glutamate to AMPARs, Na^+, K^+, and Ca^{2+} ions rapidly flow into the neuron, and depolarize the postsynaptic membranes from the resting potential[4]. The normal function of human brain depends on the balance of excitatory and inhibitory activities of neural networks. Neurons antagonize excitatory activities by upregulating the aggregation of inhibitory gamma-aminobutyric acid receptors (GABARs) on the postsynaptic membrane, so as to prevent excessive excitability of the neural network[5]. Abnormal changes in the composition, function and dynamic characteristics of AMPAR subunits will lead to a large amount of Ca^{2+} influx into dendritic cells to over activate

the downstream pathway, inhibit the inhibitory GABARs function, and over increase the excitability of neuronal networks, leading to the excitation/inhibition imbalance in brain, which may be the etiology and mechanism of epilepsy[6]. Up to now, there are only two AMPAR antagonists, talampanel and PER, which have entered clinical trials. However, development of talampanel was discontinued due to its short half-life, poor antiepileptic efficacy and serious adverse reactions showed in the results of clinical trial. PER is the second AMPAR antagonist and is the only one approved for clinical use[6].

The VNS is an adjuvant treatment approved by the United States FDA for patients ≥ 12 years of age with drug-resistant epilepsy, and was further approved for use in patients over 4 years of age in 2017. Nowadays, much evidence has supported that VNS implantation as adjuvant therapy is possibly effective in pediatric (≤ 18 years-of-age) drug-resistant epilepsy. The pooled prevalence estimates for 50% responder rate and seizure freedom at last follow-up (mean 2.54 years) were 56.4% and 11.6%, respectively[7], and VNS may have improved efficacy over time[8]. Davis Jones *et al*[9] reported that PER could further reduce the seizure frequency in a part of adult patients with drug-resistant epilepsy who still had seizures after their previous VNS implantation or resective surgery. However, no report was found about the use of PER in young children with drug-resistant epilepsy after VNS implantation. Our patient was a 4-year-old young child with multidrug-resistant epilepsy who still had frequent seizures after his VNS implantation as adjuvant therapy, and he showed significant response to PER as add-on in a dose-dependent manner, with seizures reduced by more than 80% after 7-mo treatment. Therefore, we propose that for young children with drug-resistant epilepsy who still have frequent seizures after VNS implantation, the use of PER as add-on could further reduce the seizure frequency.

Some studies have shown that PER may improve cognitive function in children patients. In a phase II randomized, double-blind, placebo-controlled study of 133 adolescent patients with uncontrolled partial-onset seizures, the systematic analysis of the Cognitive Drug Study revealed that PER may have favorable cognitive profile for adolescent population[10]. The increase of β-band in quantitative electroencephalogram

(QEEG) is related to the improvement of attention and cognitive function, and the increase of α-band is related to the impairment of cognitive function[11]. In a QEEG study on patients treated with PER, it is found that PER can increase the β-band in the occipital lobe region, without the increase of α-band, confirming the beneficial effect of PER on cognitive function, which may be mediated by its direct effect on the neurotransmission of glutamate[11]. In our case, although the quantitative scales were not evaluated in this patient before and after the treatment of PER, he showed improved cognitive skills and language according to our observation and his parents' records, which suggested the favorable cognitive profile of PER in young children.

The adverse events (AEs) of AEDs are the key factors affecting AEDs selection, patients' quality of life and long-term drug retention. The AEs of PER mainly include dizziness, irritability, fatigue, aggressiveness, suicide, nausea, weight gain, *etc.*[2] Dizziness and somnolence were the most common AEs[3]. Because of some severe mental and behavioral adverse reactions, including aggressiveness, irritability, homicidal behavior, and threats, the PER was given a black box warning by the United States FDA when it was first approved[12]. The patient in our case developed irritability and aggressive behavior after the treatment of PER, which were considered as its adverse reactions. Irritability is the most common psychotic adverse reaction, with an incidence of 2.1% to 17.9%[13]. Although the mechanism behind irritability and related aggressive behavior is unclear, serotonin, GABA, and especially glutamate (*via* the AMPAR) seems to play an important role[13]. The effects of glutamate on behavior are complex, and some animal studies have shown that blocking AMPARs can lead to increases or decreases in aggressive behavior. This indicates that the AMPAR blockage may contribute to the emotion-related adverse reactions of PER[13]. The AEs of PER are dose-dependent, and may disappear after dose adjustment or drug withdrawal[14]. It is recommended to start PER with a low dose and titrate slowly, generally adding 2 mg every 2-4 wk. Slow titration can improve the long-term tolerance of PER and reduce the incidence and severity of AEs, including psychiatric symptoms. Adverse reactions of PER can be alleviated by taking the drug before bedtime[10].

In addition, we also searched the National Library of Medicine and the China National Knowledge Infrastructure during January 10th and January 15th, 2020, with the following keywords: "perampanel AND children". Only papers on the administration of PER for multidrug-resistant epilepsy were selected. We identified the data about the efficacy and safety profile of PER in children under 12 years old with drug-resistant epilepsy (summarized in Supplementary Table 1). From most previous researches, after 3-12 mo of treatment, nearly 40%-50% or more young children showed responses to PER, and some patients could reach seizure free using PER. For patients with various genetic causes, significant seizure reduction was also reached with treatment of PER. In children under 12 years old, the incidence of AEs ranged from approximately 20% to 50%, including somnolence, behavioral deterioration, and emotional change, while no obvious AEs were demonstrated in most case reports. Furthermore, in most reported cohorts, PER possessed the similar efficacy and safety profile in children under 12 years old as in older people[15,16]. Together with this case, these results suggest that PER proves to be an effective and broad spectrum cover AED for children under 12 years old, who suffer from multidrug-resistant epilepsy, with acceptable safety profile.

CONCLUSION

In this study, we presented a 4-year-old young child with multidrug-resistant epilepsy who still had frequent seizures after VNS implantation, and he showed significant response to PER as add-on in a dose-dependent manner. We proposed that the use of PER as add-on could further reduce the seizure frequency for young children with drug-resistant epilepsy and even after VNS implantation, which may be attributed to its novel antiepileptic mechanism. Considering the similar efficacy and safety profile of PER in children under 12 years old as in older people, as well as its potential favorable cognitive profile and convenience for use, the PER should be considered as an effective and important treatment for young children with multidrug-resistant epilepsy. And the adverse reactions like irritability and aggressive behavior should be monitored during the use.

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