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Vagus nerve stimulation for pediatric patients with drug-resistant epilepsy caused by genetic mutations: Two cases

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ABSTRACT

Vagus nerve stimulation (VNS) is a neuromodulation therapy increasingly used for treating drug-resistant epilepsy. However, it remains to be determined which patients are best suited for the treatment, and it is difficult to predict the therapeutic effect before the implantation. Mutations in some genes could lead to epilepsy. Here we report two cases of pediatric patients with drug-resistant epilepsy treated by VNS therapy: Patient 1 with ARX mutation achieved good outcomes; Patient 2 with the CDKL5 mutation did not show improvement. Additionally, the therapeutic impact of VNS on brain networks was investigated, hoping to provide some empirical evidence for a better understanding of the mechanism of VNS treatment.

1 Introduction

In 1997, vagus nerve stimulation (VNS) was approved by the US Food and Drug Administration (FDA) for use in treating drug-resistant epilepsy. Since then until 2018, VNS devices have been implanted in over 80,000 patients worldwide [1]. Genetic factors play a crucial role in the pathogenesis of epilepsy. In the few monogenic forms of symptomatic epilepsy, X-linked cyclin-dependent kinase-like 5 (CDKL5) and aristaless-related homeobox (ARX) genes were found to be responsible for X-linked epileptic encephalopathies associated with early-onset seizures and drug-resistant myoclonic epilepsy [2]. Studies on using VNS therapy in treating gene-related epilepsy are limited. In this paper, two cases were reported: a 4.2-year-old girl with an ARX mutation who experienced a good reduction in seizure frequency

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and a 3.3-year-old girl with a CDKL5 mutation who showed no reduction in seizure frequency following the initiation of VNS therapy.

2 Case report

2.1 General information

Patient 1 was a 4.2-year-old girl, the younger child of fraternal twins, born by C-section at 37 weeks of gestation with a birth weight of 2.3 kg. During pregnancy, she was physically healthy with no history of hypoxic-ischemic encephalopathy at birth. She was born to non-consanguineous parents with no family history of epilepsy or neuropsychiatric disorders. At the age of 6 months, an unprovoked nodding spasm began to occur in clusters, and from then on, her psychomotor development was delayed. Brain magnetic resonance imaging (MRI) at the ages of 6 months, 2 years, and 4 years did not reveal remarkable findings. Hypsarrhythmia and epileptic spasms were detected by the initial electroencephalogram (EEG). One month before initiating VNS therapy, the interictal EEG showed generalized polyspikes and waves in the background (Fig. 1) and generalized spikes activities during sleep, while ictal EEG detected generalized fast activities in cluster, synchronized with each nodding. A de novo mutation in the ARX gene (c.1151G>A, p.R384H) was spotted by genetic testing. Moreover, Sanger sequencing of the ARX gene was negative for her fraternal twin sister. At the time of seizure onset, the patient was diagnosed with epileptic spasms, evolving gradually to Lennox-Gastaut syndrome at 2.5 years old.

![Fig. 1 Interictal EEG of Patient 1 and Patient 2 before and after VNS therapy. (A) and (B) EEG of Patient 1 showed generalized polyspikes and waves before VNS and 6 months after VNS. (C) and (D) EEG of Patient 2 showed generalized polyspikes and waves before VNS and 6 months after VNS.](image-url)
Patient 2 was a 3.3-year-old girl, born at 40 weeks and 2 days of gestation. Her mother had gestational diabetes. Before her birth, the fetal heart rate declined to 100 beats per minute (bpm), which resulted in an emergency C-section. She was born to non-consanguineous parents with no family history of epilepsy. Seizures’ onset occurred on day 18 after birth; subsequently, her psychomotor development was delayed. Brain MRI was performed five times from the onset of seizures to the time of starting VNS therapy, showing unremarkable results. The initial EEG recorded hypsarrhythmia and epileptic spasms, while repeated EEG at the time of VNS detected the occurrence of interictal generalized polyspikes and waves (Fig. 1). Three types of seizures were recorded in this case, including epileptic spasms, focal seizures, and myoclonic seizures. A missense mutation in the CDKL5 gene (c.134A>T; p.L45M) was spotted by gene testing. She was diagnosed with West syndrome and did not respond well to the antiepileptic drugs used before starting VNS therapy. The demographic and clinical characteristics of the two patients are listed in Table 1.

2.2 Vagus nerve stimulation therapy

From December 2017 to August 2018, the two patients took part in a multicenter, double-blind clinical trial for assessing the safety and effectiveness of VNS for children with intractable epilepsy, where they received surgeries for VNS system implantation (G112, Beijing PINS Medical Co., Ltd., Beijing, China). The follow-up period was 26 weeks [3]; after the VNS system implantation procedure, the patients were followed up at 8, 14, 20, and 26 weeks. Initial stimulation was performed for two weeks postoperatively with the following conditions: a current output of 0.5 mA, frequency of 30 Hz, the pulse width of 500 μs, 30 s of signal-on time, and 5 min of signal-off time. During the 26-week follow-up period, only

| Case | Patient 1 | Patient 2 |
|------|-----------|-----------|
| Gender | Female | Female |
| Age at start of the study | 4.2 years | 3.3 years |
| Age at onset of seizures | 6 months | 18 days |
| Variant site | ARX (c.1351G>A; p.R384H) | CDKL5 (c.134A>T; p.L45M) |
| Variant type | de novo; missense | de novo; missense |
| Seizure type | Focal seizure; spasm seizures; tonic seizures | Focal seizure; spasm seizures; myoclonus seizures |
| MRI | Normal | Normal |
| EEG | Hypsarrhythmia → generalized polyspikes and waves | Hypsarrhythmia → generalized polyspikes and waves |
| Epileptic syndrome | West syndrome → Lennox Gastaut syndrome | West syndrome → Lennox Gastaut syndrome |
| Therapy history | VPA; ACTH; LEV; OXC; TPM; VGB; CLB; KD | VPA; LEV; ACTH; OXC; LTG; TPM; CLB; KD |
| Seizures frequency at baseline | 90/month | 90/month |
| Seizures frequency at 6-month follow-up | 18/month | 95/month |
| Reduction in seizures | 78% | ~5% |

VPA: sodium valproate; ACTH: adrenocorticotropic hormone; LEV: levetiracetam; OXC: oxcarbazepine; TPM: topamax; VGB: vigabatrin; CLB: clobazam; KD: ketogenic diet; LTG: lamotrigine.
the stimulus current magnitude was adjusted, while the other parameters remained unchanged.

Patients’ diaries were utilized to assess the efficacy of VNS treatment. Routine EEG registrations were recorded before implantation and at 26-week follow-up. The Ethics Committee of the Shenzhen Children’s Hospital approved the data collection and analysis.

2.3 Brain network analyses
Quantitative EEG (qEEG) analysis was conducted. EEG blocks from eyes-open resting state were quantitatively analyzed using MATLAB toolboxes: EEGLAB [4] and ENA (http://www.neuro.uestc.edu.cn/name/shopwap/do/index/content/319). The EEG data processing steps are shown in Fig. 2. The properties of the brain network, such as clustering coefficient (C), local efficiency (Le), characteristic path length (L), and global efficiency (Ge), were evaluated before the surgery and at 26-week follow-up based on coherence and phase-locking value (PLV) within δ (1–4 Hz), θ (4–8 Hz), α (8–14 Hz), β (14–30 Hz), and β1 (14–20 Hz) bands.

3 Results
The changes in seizure frequency and current output are displayed in Fig. 3. In the case of Patient 1, after 14 weeks, the stimulation current output was elevated to 1.8 mA, and seizure frequency was markedly reduced from about three times per day to less than once a day. In the case of Patient 2, when the current output reached 1.5 mA for the first time, the seizure frequency decreased by approximately 30%; however, it gradually increased when the current output was set to 1.8 mA. Even after the current was set back to 1.5 mA at 20-week follow-up, the seizures’ frequency still continued to increase. After six months of VNS therapy, seizures’ frequency of Patient 1 decreased by 78% compared to the baseline, while Patient 2 experienced no improvement (Table 1). Table 2 listed the VNS parameters at 26-week follow-up.

Regarding the visual examination, in the two patients, there was no significant change in the overall impression of the EEG. Additionally, qEEG analysis was carried out. Figure 4 illustrated the changes in the characteristics of the brain network. Compared with baseline, both patients’ brain networks demonstrated the same trend in the β and β1 bands, such as an increase in clustering coefficient, an increase in local efficiency, a decrease in characteristic path length, and an increase in global efficiency, indicating that, after VNS treatment, the brain network’s global parallel information processing and transmission capacity might become stronger.

Fig. 2 EEG data processing process. REST, technique standardization electrode reference [5, 6].
Fig. 3 The seizure frequency of Patient 1 and Patient 2 over time. Red circles mean that the VNS setting is adjusted at this point, and the adjustments of current output are displayed in the red dotted box beside the circle. The stimulating current for Patient 1 was increased to 1.5 mA two weeks after the startup of the VNS system, remained unchanged until 14-week follow-up, and increased to 1.8 mA at 14-week follow-up. The stimulating current for Patient 2 was increased to 1.5 mA two weeks after startup, remained unchanged until 14-week follow-up, and then increased to 1.8 mA. Due to the gradual increase in seizures frequency, the stimulating current was decreased back to 1.5 mA at 20-week follow-up.

Table 2 Stimulator parameters in two cases at 26th-week follow-up.

| Parameters                  | Patient 1 | Patient 2 |
|-----------------------------|-----------|-----------|
| Output current (mA)         | 1.8       | 1.5       |
| Signal frequency (Hz)       | 30        | 30        |
| Pulse width (μs)            | 500       | 500       |
| Signal on time (s)          | 30        | 30        |
| Signal off time (s)         | 300       | 300       |
| Magnet output current (mA)  | 2.0       | 1.7       |
| Magnet pulse width (μs)     | 500       | 200       |
| Magnet signal on time (s)   | 30        | 30        |

4 Discussion

Two cases with drug-resistant epilepsy caused by different genetic mutations were reported. Both were treated with VNS therapy, yet had different outcomes. After six months of VNS treatment, Patient 1 demonstrated a reduction in seizures’ frequency by 78% compared to the baseline, while Patient 2’s condition did not improve. We followed up with the patients through phone calls after 26 weeks. At 15-month follow-up by telephone interviews, Patient 1 was seizure-free, while Patient 2’s state remained unchanged. From the end of the 26-week follow-up period until the telephone interview, the stimulation parameters and medications were not adjusted for both patients owing to personal reasons. The poor outcomes in Patient 2’s case could be attributed to a failure in adjusting the suitable parameters for her condition. Nevertheless, this may indicate that if the patient did not respond to a specific setting in the short term, the stimulation would not work and their condition will remain the same as time passes. Improving the patients’ compliance when adjusting the parameters of VNS should be considered; for example, establishing a remote parameter adjustment platform could allow patients to adjust settings at home.

Physicians must find the correlation between drug-resistant epilepsy associated with genetic mutations and the efficacy of VNS therapy as it is important when assessing and choosing the suitable treatment for their patients. In the literature, reports about the efficacy of VNS in reducing seizures in patients with drug-resistant epilepsy due to gene mutations are limited [7–11]. Most of these researchers examined the relationship between CDKL5 and neuronal voltage-gated sodium-channel alpha-subunit (SCN1A) genes and epilepsy. Stephen et al. [7] conducted a retrospective review of 20 pediatric patients with malignant mutations in SCN1A who underwent VNS treatment for drug-resistant epilepsy. At 6-month follow-up, 9 patients showed improvement with > 50% reduction in generalized tonic-clonic seizures; 4 patients reported improvement in cognitive or speech development; 7 patients who had their
VNS implanted at other institutions reported subjective benefit, with 4 indicating “marked improvement” or seizure freedom. The efficacy of VNS in patients with CDKL5 gene mutations was examined previously [11]. Lim et al. surveyed 222 patients: only 17.1% were treated with VNS therapy and more than two-thirds of the patients showed improvement in seizure control with VNS, but none of them became seizure-free [11].

In a retrospective multicentered study, 347 children with predominantly generalized seizures caused by genetic and structural epilepsy, such as Dravet syndrome or Lennox-Gastaut syndrome, received VNS treatment and reported favorable outcomes, but the improvement was marginally lower compared to the entire population [12]. Unfortunately, Patient 2 did not show any improvement regarding seizure control with VNS therapy.

ARX mutations are more common in men than in women. Phenotypic polymorphism associated with X-linked dominant ARX mutations has been well documented; however, heterozygous female carriers were not thoroughly studied [13]. ARX is crucial for the interneurons’ development in deep gray matter, cerebral cortex, and hippocampus [14, 15].

Patient 1 presented with West syndrome and infantile epileptic encephalopathy; such phenotypes are consistent with the mutations in the ARX gene, usually resulting in drug-resistant epilepsy and unfavorable outcomes. To the best of our knowledge, this is the first case report about a female patient (Patient 1) with ARX mutation treated by VNS.

Mutations in ARX and CDKL5 genes can result in various brain disorders, further leading to significant differences in brain networks. EEG could reveal the therapeutic efficacy of VNS. Baba et al. [8] reported one case of an 8-year-old girl with a CDKL5 mutation who underwent
VNS therapy for two years. After two years of VNS therapy, her seizure frequency was markedly reduced, there is an improvement in EEG background slowing, paroxysmal high-voltage slow waves disappeared, and abnormal electrical activities strikingly decreased. From the conventional point of view, in our study, there was no significant change in the overall impression of the EEG in the two patients, which could be attributed to the short duration of VNS treatment (only six months). However, by comparing brain networks’ properties before and after the VNS operation, the qEEG revealed that the global parallel information processing and transmission capacity in both patients’ brain networks were relatively stronger after six-month VNS treatment, potentially proving the efficacy of the therapy.

Epilepsy is now increasingly considered as a disorder of brain network connectivity [16]. Studying if VNS therapy can induce the reorganization of a functional brain network is vital. In the last few years, the correlation between clinical improvement generated by VNS therapy and topological changes in brain networks was explored [16–22]. In the study by Fraschini et al., the EEG recordings of ten patients with drug-resistant epilepsy were analyzed and the functional connections between EEG signal channels were estimated using the phase lag index (PLI) [19]. The findings showed that, as a result of VNS therapy, functional brain networks were reorganized and rearranged to a more effective (i.e., more integrated) network structure, and these VNS-induced alterations were associated with the observed clinical improvements. Wang et al. constructed brain networks from EEG signals of 20 pediatric patients with Dravet syndrome by comparing the recordings before treatment and after 6 months, 12 months, and 24 months of VNS therapy [22]. They noticed that, in α and β bands, after 6 months of VNS therapy, characteristic path length decreased, global efficiency increased, and transitivity increased in both responders and nonresponders. Our findings revealed that the brain network’s functional efficiency was enhanced compared with baseline in both patients (even though Patient 2 is a nonresponder); this is consistent with Wang et al.’s results in β band, but no significant change was observed in α band. It was shown previously that VNS can have acute or chronic effects on the EEG rhythms of adult patients with drug-resistant epilepsy, mainly, in δ band [17], θ band [19, 21], α band [21], or γ band [16, 18]. However, in the study of pediatric patients, after VNS therapy, the EEG networks in α and β bands were changed significantly, indicating the essential difference between the adult and pediatric patients’ brain networks or between patients with different etiologies.

Brain network analyses of these two patients will provide empirical evidence for future studies. For a better understanding of the efficacy and mechanism of VNS therapy, we recommend that, in the future, brain network analysis is added to the clinical investigation of each patient receiving VNS treatment, which could offer help when managing challenging gene mutation-related epilepsy cases.

5 Conclusion

In this case report, we present two pediatric patients with two kinds of gene mutations who received VNS treatment and experienced different outcomes. Moreover, the brain network properties of the two patients changed in varying degrees after 6 months of VNS therapy. Further prospective or retrospective studies should be conducted to examine the correlation between drug-resistant epilepsy due to different gene mutations and the efficacy of VNS and the
impact of VNS therapy on brain network.

Conflict of interests

The authors declare no conflict of interests in this work.

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References

[1] Brázdil M, Doležalová I, Koritáková E, et al. EEG reactivity predicts individual efficacy of vagal nerve stimulation in intractable epilepsies. Front Neurol. 2019, 10: 392.
[2] Nabbout R, Depienne C, de Chipaux M, et al. CDKL5 and ARX mutations are not responsible for early onset severe myoclonic epilepsy in infancy. Epilepsy Res. 2009, 87(1): 25–30.
[3] Ji TY, Yang Z, Liu QZ, et al. Vagus nerve stimulation for pediatric patients with intractable epilepsy between 3 and 6 years of age: study protocol for a double-blind, randomized control trial. Trials. 2019, 20(1): 44.
[4] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 2004, 134(1): 9–21.
[5] Dong L, Li FL, Liu Q, et al. MATLAB toolboxes for reference electrode standardization technique (REST) of scalp EEG. Front Neuosci. 2017, 11: 601.
[6] Yao D. A method to standardize a reference of scalp EEG recordings to a point at infinity. Physiol Meas. 2003, 22(4): 693–711.
[7] Fulton SP, Van Poppel K, McGregor AL, et al. Vagus nerve stimulation in intractable epilepsy associated with SCN1A gene abnormalities. J Child Neurol. 2017, 32(5): 494–498.
[8] Baba S, Sugawara Y, Moriyama K, et al. Amelioration of intractable epilepsy by adjunct vagus nerve stimulation therapy in a girl with a CDKL5 mutation. Brain Dev. 2017, 39(4): 341–344.
[9] Zamponi N, Passamonti C, Cappanera S, et al. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur J Paediatr Neurol. 2011, 15(1): 8–14.
[10] Englert DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg. 2011, 115(6): 1248–1255.
[11] Lim Z, Wong K, Downs J, et al. Vagus nerve stimulation for the treatment of refractory epilepsy in the CDKL5 Deficiency Disorder. Epilepsy Res. 2018, 146: 36–40.
[12] Orosz I, McCormick D, Zamponi N, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia. 2014, 55(10): 1576–1584.
[13] Bettella E, di Rosa G, Polli R, et al. Early-onset epileptic encephalopathy in a girl carrying a truncating mutation of the ARX gene: rethinking the ARX phenotype in females. Clin Genet. 2013, 84(1): 82–85.
[14] Göcz J, Cloosterman D, Partington M. ARX: a gene for all seasons. Curr Opin Genet Dev. 2006, 16(3): 308–316.
[15] Fréoucourt G, Poirier K, Rakić S, et al. The role of ARX in cortical development. Eur J Neurol. 2006, 13(4): 869–876.
[16] Marrosu F, Santoni F, Puligheddu M, et al. Increase in 20-50 Hz (Gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. Clin Neurophysiol. 2005, 116(9): 2026–2036.
[17] Uchida T, Fujiwara K, Inoue T, et al. Analysis of VNS effect on EEG connectivity with granger causality and graph theory. In 2018 Asia-Pacific Signal and Information Processing Association Annual Summit and Conference (APSIPA ASC),
Honolulu, USA, 2018, pp 861–864.

[18] Fraschini M, Puligheddu M, Demuru M, et al. VNS induced desynchronization in Gamma bands correlates with positive clinical outcome in temporal lobe pharmacoresistant epilepsy. *Neurosci Lett*. 2013, 536: 14–18.

[19] Fraschini M, Demuru M, Puligheddu M, et al. The re-organization of functional brain networks in pharmaco-resistant epileptic patients who respond to VNS. *Neurosci Lett*. 2014, 580: 153–157.

[20] Bartolomei F, Bonini F, Vidal E, et al. How does vagal nerve stimulation (VNS) change EEG brain functional connectivity? *Epilepsy Res*. 2016, 126: 141–146.

[21] Ilyas A, Toth E, Pizarro D, et al. Modulation of neural oscillations by vagus nerve stimulation in posttraumatic multifocal epilepsy: case report. *J Neurosurg*. 2019, 131(4): 1079–1085.

[22] Wang ZJ, Kim ES, Noh BH, et al. Alteration in brain connectivity in patients with Dravet syndrome after vagus nerve stimulation (VNS): exploration of its effectiveness using graph theory analysis with electroencephalography. *J Neural Eng*. 2020, 17(3): 036014.

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