

Effects of Vagus Nerve Stimulation on Sustained Seizure Clusters: A Case Report

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Abstract

Seizure clusters (SCs) are acute repetitive seizures with acute episodes of deterioration during seizure control. SCs can be defined as a series of grouped seizures with short interictal periods. Vagus nerve stimulation (VNS) is a treatment option for drug-resistant epilepsy. We present a case where VNS suppressed epileptic SCs, which had persisted for several months. A 13-year-old boy with congenital cerebral palsy and mental retardation had drug-resistant epilepsy with daily jerking movements and spasms in both sides of his body. The seizures were often clustered, and he experienced two sustained SC episodes that persisted for a few months even with prolonged use of continuous intravenous midazolam (IV-MDZ). The patient underwent VNS device placement at the second sustained SC and rapid induction of VNS. Because the tapering of IV-MDZ did not exacerbate the SC, midazolam was discontinued 4 weeks after VNS initiation. Non-refractory SCs also disappeared 10 months after VNS. The seizure severity was improved, and the frequency of seizures reduced from daily to once every few months. The epileptic activity on electroencephalography (EEG) significantly decreased. This case highlights VNS as an additional treatment option for SC. VNS may be a therapeutic option if SC resists the drugs and sustains. Additional studies are necessary to confirm our findings and to investigate how device implantation and stimulation parameters affect the efficacy of VNS.

Keywords: sustained seizure cluster, continuous intravenous midazolam, vagal nerve stimulation

Introduction

Patients with epilepsy may experience acute repetitive seizures, which are commonly called seizure clusters (SCs). SCs can significantly impact the quality of life (QOL), psychiatric state, daily activities, productivity, studies, and work of both patients and caregivers.¹⁾

SCs are known as acute repetitive seizures with acute episodes of deterioration during seizure control.²⁾ They could be defined as a series of grouped seizures with short interictal periods.³⁾ Several studies define SCs as the occurrence of three or more seizures within 24 h (interictal period of 8 h or less).^{2–4)} Other studies propose the following definitions: two or more seizures within 6 hours,⁵⁾ two to four seizures in less than 48 h,^{2,6)} and two or more seizures over 24 h (partial or generalized), with regained consciousness between episodes.⁷⁾ Previous studies have reported prevalence rates between 13% and 76% with outpatients,^{3,4)} and rates of 18% and 61% were reported with inpatient studies with epilepsy monitoring units.^{3,8)} A population-based study in the

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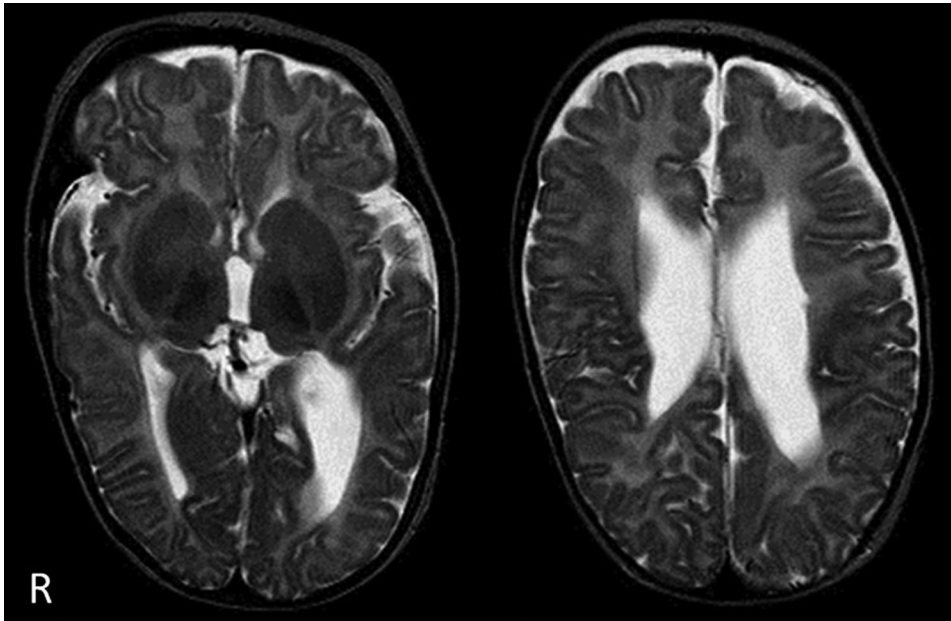


Fig. 1 Magnetic resonance T2-weighted imaging 76 days after birth detected bilateral periventricular leukomalacia.

United Kingdom reported a prevalence rate of 2.5/10,000 for SC; the study defined SC as the occurrence of three or more seizures within 24 h. The prevalence rate was 3% for patients with epilepsy.⁹⁾ The most significant risk factor for SCs is intractable epilepsy with a high frequency of seizures. SCs frequently lead to emergency room visits and also hospital admissions.^{6,10)} Status epilepticus (SE) is a condition resulting from either the failure of seizure termination mechanisms or from initiation of mechanisms that enable abnormally prolonged seizures. This condition can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks.¹¹⁾ SCs are also associated with SE. Convulsive SE occurred in 44% of patients with SCs and in 12.5% of patients without SCs in a study of patients with intractable localization-related epilepsy.¹⁾

Benzodiazepine is a rescue medication for SC.¹²⁾ Second-line therapies include intravenous (IV) fosphenytoin, valproic acid, levetiracetam, and phenobarbital. Moreover, third-line therapies, such as IV midazolam (IV-MDZ), propofol, and thiopental, may be considered if seizures continue.

Surgical therapy may be considered if drug treatments fail to suppress SC. In addition to resection surgery, neuromodulation therapies such as vagus nerve stimulation (VNS) may be feasible. VNS has been shown to decrease the frequency and severity of many types of seizures, including severe SE.^{6,13)} However, the inhibitory effects of VNS on SCs are not known. Herein, we report a case where VNS

suppressed drug-resistant epileptic SC, which had persisted for several months.

Case Report

The patient was a 13-year-old boy with spastic tetraparesis and intellectual disability, without any family history of miscarriage or child syndrome. He was born at 29 weeks 2 days of gestation with a birth weight of 1394 g. Shortly after birth, his parents noticed poor movement of his limbs. Magnetic resonance imaging (MRI) conducted 76 days after birth revealed bilateral periventricular leukomalacia (Fig. 1). He suffered from myoclonic and generalized tonic-clonic seizures, and adrenocorticotrophic hormone therapy was initiated after diagnosis of West syndrome. The therapy was effective; however, the seizures relapsed in the next year. The seizures became drug-resistant, and bilateral jerking movements and spasms appeared maximally a few times per day. He could attend a nearby school for disabled children before the first SC, although he had most severe intellectual disability with a developmental quotient under 20 and motor disability with level 5 in the Gross Motor Function Classification System. When the patient was 11 years old, he had experienced tonic seizures with upward rolling of the eyes, which lasted for about a minute. The seizures were different from the usual bilateral jerking movements and spasms. The tonic seizures were repeated several times every few minutes. Based on a diagnosis of SE, IV-MDZ and phenobarbital were introduced

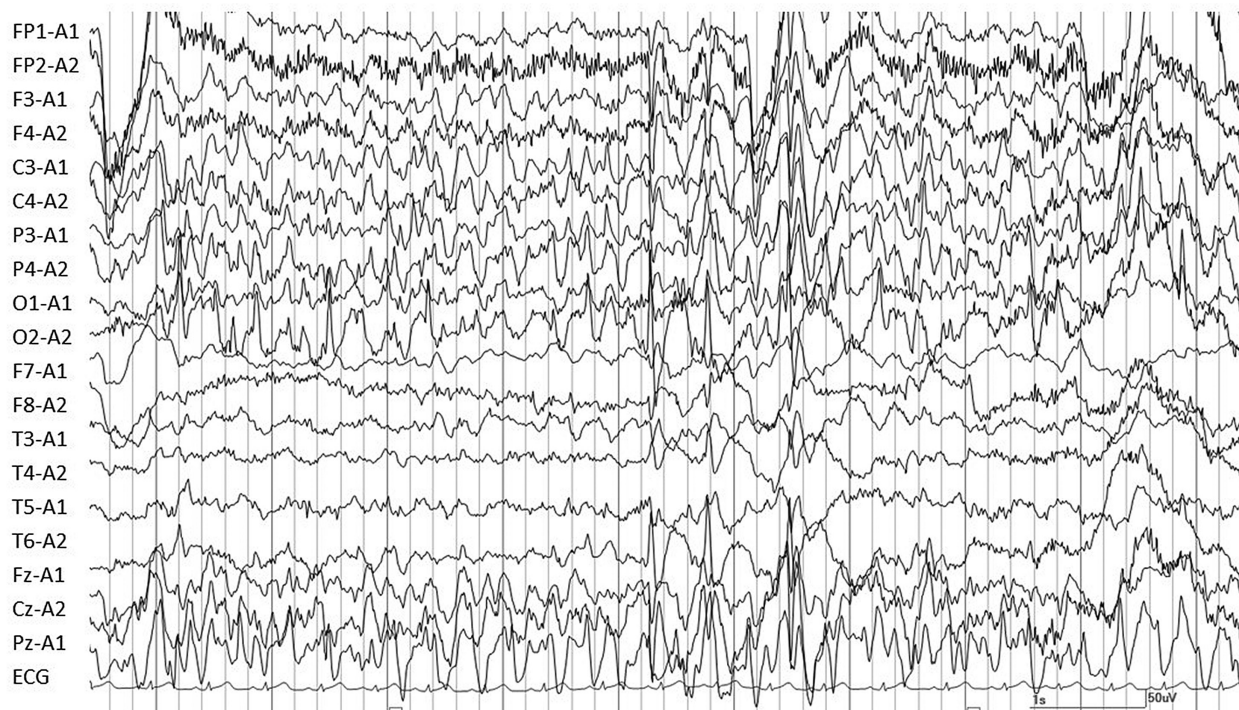


Fig. 2 Interictal awake electrocorticogram before VNS. The results revealed diffuse spikes and slow waves with bursts lasting a few seconds, predominantly in the frontal and parietal regions. VNS: vagus nerve stimulation.

without intubation. When continuous IV-MDZ was stopped 6 days later, the tonic seizures relapsed, and IV-MDZ was restarted. Interictal electroencephalography (EEG) under IV-MDZ revealed many left-dominant bilateral spikes in the parietal region; the seizures were thought to be focal to bilateral tonic seizures. Repeated EEG during sustained SCs showed similar findings. Tonic seizures lasting for 10–20 seconds appeared 2–3 times a day under continuous administration of IV-MDZ and five oral drugs (lamotrigine, phenobarbital, phenytoin, zonisamide, and topiramate). IV-MDZ at a dose of 0.125 mg/kg/h was continuously given to the patient for 3 months until the SCs disappeared. Sporadic SC, with tonic seizures that lasted less than 1 minute and repeated 2–8 times a day, began to occur 1–2 times a month after this event. Tonic seizures were sometimes repeated within an hour, and he was treated with diazepam suppositories or a single bolus of IV-MDZ in such case. Two years later, SCs occurred every day and continuous IV-MDZ was administered. Seizures occurred 2–8 times a day even under IV-MDZ. Computed tomography revealed findings similar to the MRI taken in infancy. Interictal awake EEG under IV-MDZ showed diffuse spikes and slow waves, predominantly in the parietal and occipital regions (Fig. 2). Therefore, VNS was indicated to reduce persistent SC because further

five oral drugs (perampanel, valproate, kalium bromide, gabapentine, and nitrazepam) had not been effective, and IV-MDZ administration at a dose of 0.075 mg/kg/h had been continued for more than 1 month with four oral medicines.

VNS-Aspire SR was implanted, and stimulation was started the day after surgery. Figure 3 shows the clinical course after VNS implantation. The stimulation current was increased every 2 days by 0.25 mA from 0.5 mA to 1.50 mA. Although zonisamide, clobazam, potassium bromide, and phenobarbital were continued at the same doses as before surgery, the dose of MDZ was decreased gradually over a course of 2 weeks, from 1.5 mg/h to 0.8 mg/h. EEG still showed continuous diffuse spikes and waves. MDZ was stopped 2 weeks after increasing the VNS duty cycle from 10 to 16 and increasing clobazam from 9 mg/day to 14 mg/day. SC occurred only one time during the tapering of MDZ. After that, SCs appeared 0–4 times a month, but seizures were inhibited by a single venous injection of diazepam or MDZ. Diffuse spikes and waves were decreased in conventional EEG 3 months after the initiation of VNS.

The clobazam dosage was increased up to 15 mg/day 3 months after VNS. Zonisamide was replaced by carbamazepine 7 months after VNS. The output of VNS was increased to 2.50 mA 8 months after VNS to enable a reduction in SCs. Other parameters

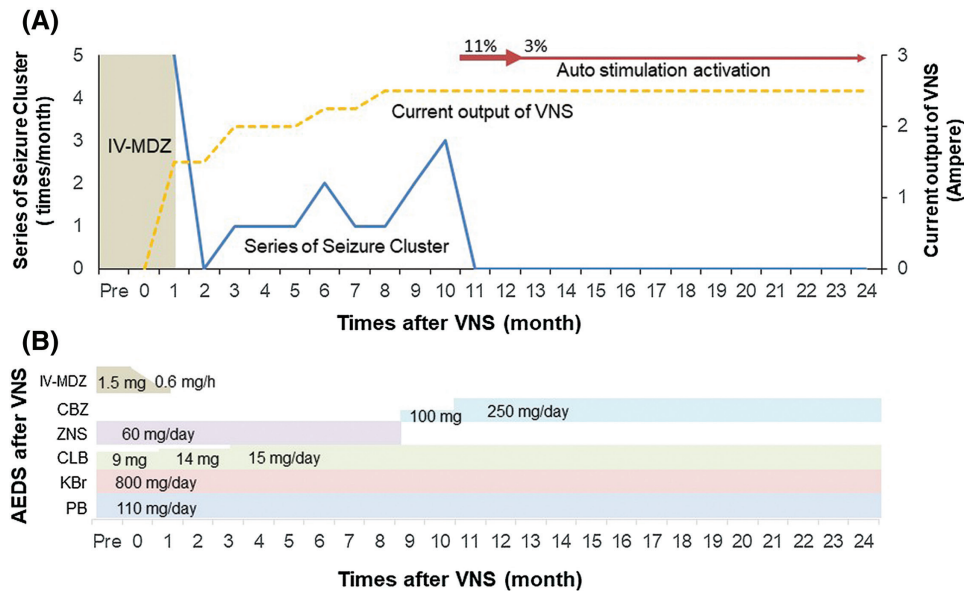


Fig. 3 Clinical course after VNS. (A) Effect of VNS on the number of SCs (solid line). The series of SCs clearly decreased after VNS. VNS output current (dotted line) gradually increased up to 2.5 mA after rapid induction up to 1.5 mA. (B) AEDs used after VNS. PB, KBr, and CLB were continued, but ZNS was replaced with CBZ until week 45 after VNS. The dose of IV-MDZ was gradually decreased and discontinued 4 weeks after inducing VNS. AEDs: anti-epileptic drugs, CBZ: carbamazepine, CLB: clobazam, IV-MDZ: intravenous midazolam, KBr: potassium bromide, PB: phenobarbital, SCs: seizure clusters, VNS: vagus nerve stimulation, ZNS: zonisamide.

were as follows: 30-Hz frequency, 500- μ sec pulse width, 30-s on-time, 1.8-min off-time, auto stimulation mode (sense 3, HR +30%, output 2.5 mA, 60 sec), and magnet mode (2.75 mA, 30-Hz frequency, 500- μ sec pulse width, 30-s on-time, 1.8-min off-time). Auto stimulation mode was introduced at this point (sense 3, HR +20%, output 1.5 mA, 60 s). SC completely disappeared 10 months after VNS, and auto stimulation was used at 11% of the 2-month observation period. The parameter of auto stimulation mode was changed slightly (sense 3, HR +30%, output 1.5 mA, 60 s). One year after surgery, seizures also decreased to once in a few months (McHugh class 1).¹⁴⁾ The magnet mode was used only a few times in a month, and was no longer used after 10 months of implantation. The patient was able to return to his special education school, and the actuation of auto stimulation mode was less than 3% during the 16 months after VNS. EEG performed 21 months after VNS revealed that the spike waves had disappeared, and the frequency of sporadic spikes had decreased (Fig. 4).

Discussion

In case SCs persist despite the use of drugs, additional treatments are required. Neuromodulation therapies, such as VNS, deep-brain stimulation, and

responsive neurostimulation, are feasible treatment options for refractory SCs. VNS is the most popular among these neuromodulation therapies. Long-term studies in heterogeneous populations of patients with drug-resistant epilepsy have shown that VNS elicits a >50% reduction in seizure frequency in approximately 60% of patients.^{15,16)} Some studies also note that the addition of VNS allows weaning or discontinuation of antiepileptic medications.¹⁷⁾ VNS is hypothesized to control seizures by sending regular pulses to the brain through stimulation of the vagus nerve. EEG studies using different measures of synchronization suggest that VNS may acutely desynchronize the interictal EEG, which may impede the development of hypersynchronous rhythms.¹⁸⁾ VNS also acutely desynchronizes ictal rhythms, which inhibits the propagation of focal-onset seizures.¹⁸⁾

Underlying mechanisms of VNS remain unclear. VNS has been shown to increase firing rates and metabolic activities in the nucleus tractus solitarius of the brainstem and other structures directly connected to it.¹⁹⁾ Among these structures, the dorsal raphe nucleus and locus coeruleus of the brainstem are of special interest because they are the main sites of serotonin and norepinephrine production in the brain. Increased levels of these monoamines and their metabolites have been found in patients treated with VNS and in preclinical studies involving VNS.^{20,21)}

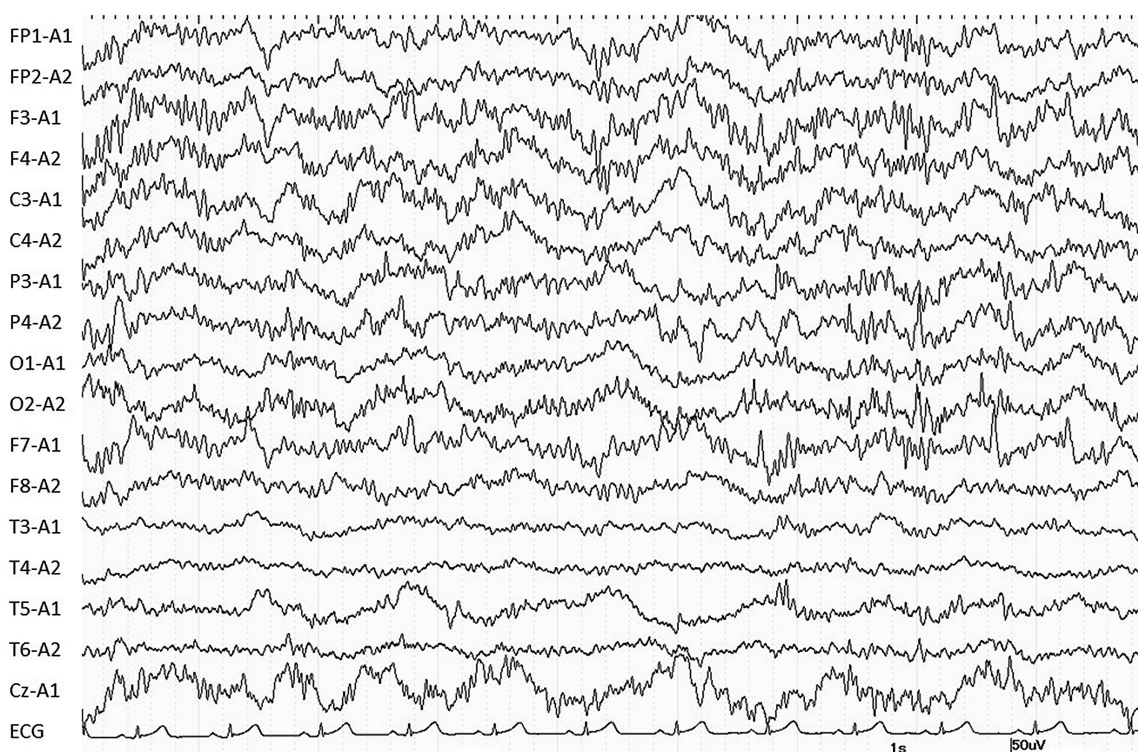


Fig. 4 Interictal awake electroencephalogram 21 months after VNS. Spikes and waves seen before VNS disappeared during the recording; however, sporadic spikes still appeared. VNS: vagus nerve stimulation.

Refractory SE (RSE) is defined as the persistence of SE despite treatment with benzodiazepines, used as first-line treatment, and one antiepileptic drug, administered as second-line treatment. RSE occurs in approximately 30% of patients with SE. Super-refractory SE (SRSE) is characterized by ongoing SE despite 48 h of anesthetic treatment.^{22,23)} VNS interrupted 76% of the general and 26% of the focal RSEs,²⁴⁾ and acute VNS implantation was associated with cessation of RSE/SRSE in 74% (28/38) of acute cases.¹³⁾ The difference of the etiology between RSE/SRSE and sustained SC is not clear, but VNS is expected to be effective for refractory SC as a therapeutic option because of its effectiveness for RSE/SRSE. A similar therapeutic strategy is proposed for sustained SC and SE including RSE/SRSE. Similarly, a ketogenic diet (KD) may become another treatment option for sustained SC because a case series of 14 pediatric patients with RSE reported that KD resolved electrographic seizures, with >50% suppression in 10/14 patients within 7 days of starting the KD. In total, 11 of 14 patients were weaned off continuous infusions within 2 weeks after starting the KD.²⁵⁾ In contrast, children with developmental delays often experience multiple seizures per day and often experience repeated seizures in a short

period of time. Additional criteria may be required to distinguish SCs from SE in these patients. This issue requires further discussion.

Multiple drugs may be used in the treatment of repetitive SC. The toxicity associated with the use of multiple drugs and respiratory problems occurring with the use of sedative drugs could increase the mortality rate due to SCs.³⁾ Furthermore, prolonged use of IV-MDZ decreases QOL and causes comorbidities such as respiratory and feeding problems, even if the seizure is controlled. VNS instead of prolonged IV-MDZ could improve patient QOL as well as provide seizure control.

Conclusions

This case highlights VNS as an additional treatment option for SCs. Indication of VNS should be considered in the case of recurring SCs. However, additional research regarding device implantation and stimulation parameters is necessary to determine its therapeutic efficacy.

Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare.

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