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CASE REPORT

Aggravation of seizures and status epilepticus after vagal nerve stimulation therapy: the first pediatric case and review of the literature

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Abstract

Background We describe the first child with drug-resistant epilepsy in whom vagus nerve stimulation aggravated seizures and emerged status epilepticus after the increase in vagal nerve stimulation current output.

Objective A 13-year-old girl presented with refractory secondary generalized focal epilepsy. Vagal nerve stimulator was implanted because of drug-resistant epilepsy. After the increase of vagal nerve stimulator current output to a relatively high level, the patient experienced seizure aggravation and status epilepticus.

Conclusion We conclude that vagus nerve stimulation may induce paradoxical seizures and may lead to status epilepticus, similarly to some antiepileptic drugs.

Keywords Epilepsy · Seizures · Vagal nerve stimulation

Introduction

Vagal nerve stimulation (VNS) is an effective adjunctive therapy for pediatric patients with drug-resistant epilepsy that is not suitable for resective surgery. The exact pathway through which the antiepileptic effect of VNS is obtained is not yet clear [1, 2]. Dysphonia, throat pain, neck pain, and coughing during stimulation are the most commonly reported side effects of VNS [3]. In our experience and according to the literature, VNS is not known to aggravate seizures in children. To our knowledge, we describe the first pediatric case with the emergence of recurrent partial seizures and status epilepticus after the increase in current output to a relatively high level in VNS therapy. Even so there are two papers, none of them in pediatric patients, reporting seizure aggravation after the initiation of VNS therapy [4, 5].

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Case report

We report on a 12-year-old girl whom seizures begun at the age of 5 years of age with complex partial seizures and drop-attacks. Her past medical history was remarkable for HSV-1 encephalitis at the age of 13 months. Despite appropriate antiepileptic drugs, her seizures worsened with secondary generalization. She was taking levetiracetam (1000 mg), carbamazepine (800 mg), and clobasam (10 mg). Brain MRI demonstrated left parietooccipital encephalomalasia (Fig. 1).

When she was 11, because of her persistent seizures, a number of diagnostic tests were performed for presurgical work up in the epilepsy monitoring unit (EMU) study. During the 4-day EMU study, four brief seizures were recorded. The clinical features included axial spasm and left-sided asymmetrical tonic seizure, lasting about 1 min. The corresponding ictal EEG revealed rhythmic discharges in the left frontotemporal region predominantly with 2–3-s attenuation (Fig. 2). MR-tractography revealed that the lesion is very close to the visual area. The patient was informed about the results of the video EEG monitoring and was discharged home on titration schedules of carbamazepine and levetiracetam. On further follow-up visits, the patient's seizures did not respond to antiepileptic drugs. The patient was discussed in Epilepsy Surgery Meeting and because of localization of the lesion, agreed on vagal nerve stimulation trial. Because of failure of multiple antiepileptic drugs, a VNS (Cyberonics Model 103) was implanted on the left vagal nerve. The initial VNS



Fig. 1 Brain magnetic resonance imaging showing left parietooccipital encephalomalacia

parameters were set as follows: stimulus output current at 0.25 mA, pulse width at 250 μs, frequency of 30 Hz, on cycle of 30 s every 5 min off.; subsequently, the current was gradually increased in regular visits to assess efficacy. AED regimen remains unchanged, and at each visit VNS parameters were changed according to the estimated seizure frequency and severity based on parents seizure calendar. Three months after implantation and on "normal cycling" (30 s on; 5 min off) stimulation at 1.5 mA, her seizures had been reduced by 40% with VNS and VNS functioning was uneventful. The current was subsequently increased to 2.0 mA with a view to possibly switching to the "rapid cycling" mode (5 s on; 30 s off) in order to obtain a better seizure control.

One day after this increase, the patient developed secondary generalized clonic seizures on the left side of her face and was hospitalized because of the status epilepticus. Intravenous diazepam, phenytoin, and continuous midazolam infusion were used to control the seizures with a moderate decrease in seizure frequency. The VNS was suspected to be the cause of status epilepticus. Therefore, it was decided to turn off the VNS and she had no generalized tonic clonic seizures. The seizures decreased gradually and subsided after 1 day. In the next 2 days, VNS was kept off and only a few brief seizures occurred despite the withdrawal of midazolam infusion and parenteral AEDs. After 3 days, a trial of VNS was made to confirm the exact relationship between VNS and status epilepticus. VNS was reactivated using the initial settings for magnet current output was set at 0.25 mA, and the patient was kept in the intensive care unit during this time. Her seizures settled down. The patient was discharged with initial settings for magnet current output set at 0.25 mA. It was very slowly increased up to 1.75 mA normal cycling in 2 months and kept in this level. After 6 months of follow-up, the patient only had a few brief asymmetrical tonic seizures. For the past 1 year, the patient has been stable on AED and VNS (1.75 mA).

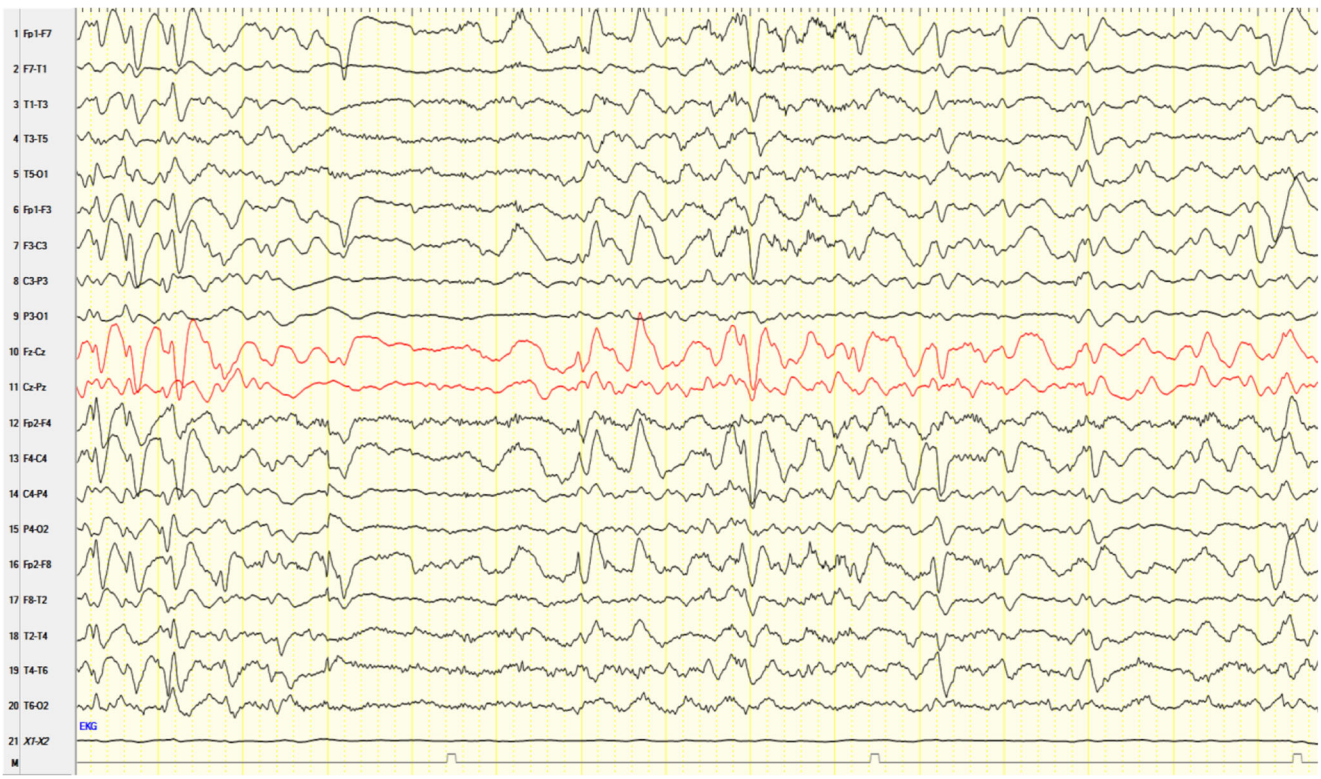


Fig. 2 Ictal EEG showing rhythmic discharges in the left frontotemporal region predominantly with 2–3-s attenuation

Table 1 Characteristics of seizure aggravation under VNS treatment in our patient and reported patients

Author	Gender (age, years)	Type of epilepsy	Time to seizure aggravation from implantation	SC (mA)
Koutroumanidis M (2000)	Female (20)	Occipital lobe epilepsy	4 months	2.5
Murr NI (2011)	Male (51)	Partial epilepsy	3 days	0.5
Our patient	Female (12)	Partial epilepsy	3 months	2

SC stimulation current intensity at the time of seizure aggravation

Discussion

To the best of our knowledge, this is the first pediatric case of aggravation of the seizures and occurrence of status epilepticus with a further increase of the current to a relatively high level (2.0 mA, normal cycling) in the absence of any other factor that might be a reason for seizure aggravation and status epilepticus.

The first reported adult case with the aggravation of the preexisting seizures due to VNS occurred after the increase of the generators current output from 2.25 to 2.50 mA on the 4th month of the stimulation. Similar to our case, seizures stopped after the discontinuation of VNS [5]. The second case with the emergence of new seizure type due to VNS was reported in 2011 [4]. In this case, the new seizures have appeared as a result of the dose titration of the stimulator to an output current of 0.5 mA (Table 1).

Despite many decades of research in clinical neurophysiology, our understanding of the mechanisms of status epilepticus remains crude. Classical phases of status show the same degree of synchrony or desynchrony that is seen in a single seizure, but the possibility that failure to reach sufficient synchrony may prevent the seizure from terminating [6, 7]. Different treatment options including VNS in a few cases have been reported in the literature; however, status epilepticus due to VNS has not been described till now. The therapeutic effect of VNS is thought to be the result of the intervention of desynchronization of the EEG activity. There is no plausible mechanism for VNS causing status epilepticus, however. The occurrence of status epilepticus after the increase in the current output of VNS may be, in theory, the result of continuous synchronization of specific structural networks, facilitating the propagation of previously dormant or inactive potential epileptogenic foci [6]. This may occur at different current outputs, the low-current output (0.25–0.50 mA) and the high-current output (2.5 mA) as in ours [4, 5]. Whenever the patient immediately develops status epilepticus, VNS should be questioned. To avoid the complications of the surgery that the patient is subjected to, combination of different stimulation parameters should be tried before the removal of the stimulator.

In conclusion, patients should be cautioned and monitored for status epilepticus or aggravation of seizures after VNS implantation. This first pediatric case report illustrates that seizure aggravation and status epilepticus is a rare but nevertheless recognized adverse event that can occur with VNS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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