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The therapeutic effect of vagus nerve stimulation on super-refractory nonconvulsive status epilepticus

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Abstract

Super refractory status epilepticus (SRSE) is a condition in which status epilepticus persists despite 48 hours of anesthetic treatment. Nonconvulsive status epilepticus (NCSE) is characterized by seizures lasting more than 30 min on an electroencephalogram, with accompanying changes in behavior or consciousness without convulsions. Prompt treatment of NCSE is crucial, as delayed treatment may lead to additional brain damage and progression to convulsive status epilepticus. Although vagus nerve stimulation (VNS) has been approved as an adjunct treatment for drug-resistant epilepsy, it is rarely used to treat refractory status epilepticus. To the best of our knowledge, only two cases of NCSE treated with VNS have been reported to date, and these patients were successfully treated with VNS for NCSE caused by anti-NMDAR encephalitis. We report the case of a patient with posttraumatic epilepsy who developed super refractory-NCSE after convulsive status epilepticus and was successfully treated with VNS.

Keywords: Status epilepticus, nonconvulsive status epilepticus, vagus nerve stimulation

INTRODUCTION

Vague nerve stimulation (VNS) was approved as an adjunctive therapy for drug-resistant epilepsy in Europe in 1994, followed by the United States in 1997 and the Republic of Korea in 1999.[1] Although some evidence suggests that VNS reduces the occurrence and recurrence of status epilepticus (SE)[2,3], whether the acute implantation of VNS during an episode of SE can be beneficial in terminating the episode is unknown. According to a systematic review of 45 patients with refractory SE (RSE) and super-refractory SE (SRSE), 38 patients underwent acute VNS implantation, and 28 (74%) experienced SE cessation.[1] Nonetheless, there are very few cases of acute implantation of VNS in nonconvulsive status epilepticus (NCSE).[4,5] Here, we present a case of a patient with post-traumatic epilepsy and super-refractory nonconvulsive status epilepticus (SR-NCSE) successfully treated with VNS.

CASE REPORT

A 37-year-old male with epilepsy secondary to post-traumatic brain injury presented with a 3-day history of generalized tonic-clonic seizures. Upon arrival, his vital signs were as follows: blood pressure of 110/67 mmHg, pulse rate of 73 beats/min, respiratory rate of 16 breaths/min, and body temperature of 37 °C. His anti-seizure medication (ASM) regimen included 400 mg topiramate, 2 mg clonazepam, 120 mg phenobarbital, and 10 mg perampanel per day. A brain magnetic resonance imaging (MRI) revealed right frontal encephalomalacia, which may be the focus of the continuous seizures. Cerebrospinal fluid testing was not performed. There were no significant

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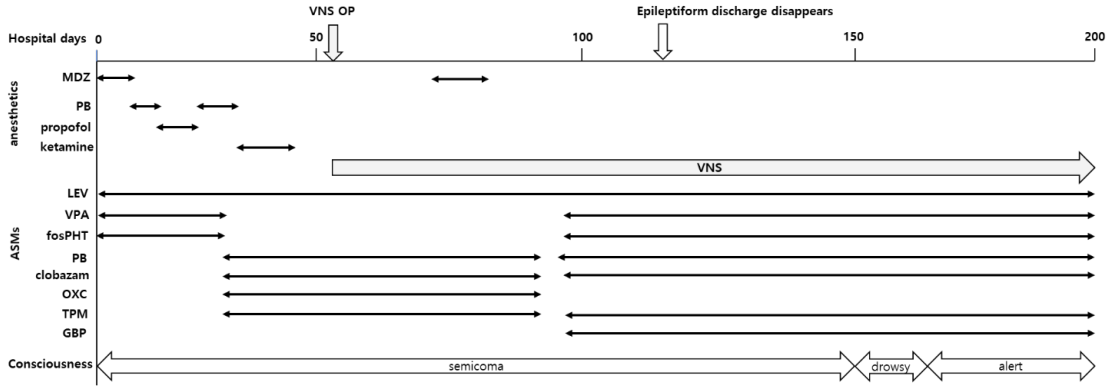


Figure 1. Timeline of hospital course. Various ASMs and anesthetics were used in the patient with SR-NCSE. VNS surgery was performed in the second month of hospitalization. On the 70th day after maximal VNS stimulation, the epileptiform discharge disappeared on the EEG, and the level of consciousness improved to alertness. ASMs, antiseizure medications; SR-NCSE, super refractory-nonconvulsive status epilepticus; VNS, vagus nerve stimulation; EEG, electroencephalogram; MDZ, midazolam; PB, phenobarbital; LEV, levetiracetam; VPA, valproic acid; fosPHT; fosphenytoin, OXC; oxcarbazepine, TPM, topiramate; GBP, gabapentin

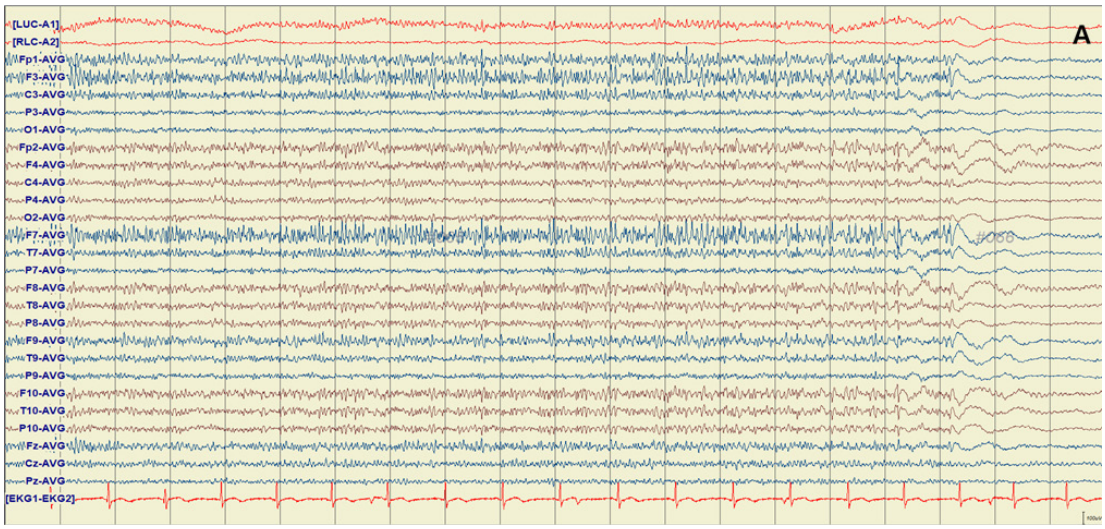
abnormalities in blood parameters aside from infection markers associated with aspiration pneumonia. Convulsive seizures stopped after the intravenous administration of lorazepam and levetiracetam at loading doses. However, continuous electroencephalography (EEG) monitoring confirmed repeated electrographic seizure discharges, and the patient was diagnosed with NCSE.

Despite anesthetic treatment with midazolam, phenobarbital, propofol, and ketamine, there were persistent electrographic seizures and no improvement in the consciousness level. After 2 months of no improvement with various anesthetic treatments, non-pharmacological treatment was considered, and acute VNS implantation was eventually performed. One week after surgery, VNS was initiated with levetiracetam 2000 mg, phenobarbital 1600 mg, pregabalin 900 mg, clobazam 40 mg, lacosamide 600 mg, topiramate 400 mg, and diazepam continuous infusion 80 mg/day. The stimulation intensity (current output) and stimulation cycle (duty cycle) were adjusted faster than in the typical schedule applied to patients with drug-resistant epilepsy. Starting from 0.5 mA, the stimulation intensity was increased by 0.25 mA each day, finally reaching 2.25 mA in 10 days. The stimulation time started at 30 s and finally increased to 60 s, whereas the non-stimulation time started at 5 min and finally decreased to 1.8 min. There were no side effects of the VNS surgery or rapid titration of VNS performed during SR-NCSE. After reaching the final target stimulation intensity and time, midazolam loading treatment was repeated, and levetiracetam 3000 mg, valproic acid 1800 mg, clobazam 30 mg, phenobarbital 400 mg, topiramate 400 mg, pregabalin 600 mg, and fosphenytoin 900 mg were administered daily. The electrographic seizures improved after 2.5 months, and he regained consciousness at 4 months post-VNS implantation. He was subsequently weaned off the ventilator and transferred to a rehabilitation hospital. (Figure 1, 2)

DISCUSSION

We attempted VNS as a non-pharmacological treatment option for SE in a patient who was being treated for SR-NCSE for more than 2 months after convulsive SE. Despite the use of various ASMs and general anesthetic agents for 2 months after conversion to NCSE, there was no recovery of consciousness, and repeated electrographic seizures were confirmed on EEG; therefore, VNS treatment was planned. At 2.5 months after VNS surgery, electrographic seizures disappeared from the EEG. Four months after the surgery, his consciousness improved, and he was able to communicate; subsequently, the ventilator was removed, and he was transferred to a rehabilitation hospital. The typical duty cycle of VNS applied to patients with DRE is 10%.[6] The case we present was treated with a stimulation time that increased more than three times the typical duty cycle to 36%. Although the titration was a relatively rapid and high-duty cycle, no specific adverse effects were observed.

Treating RSE and SRSE can be challenging,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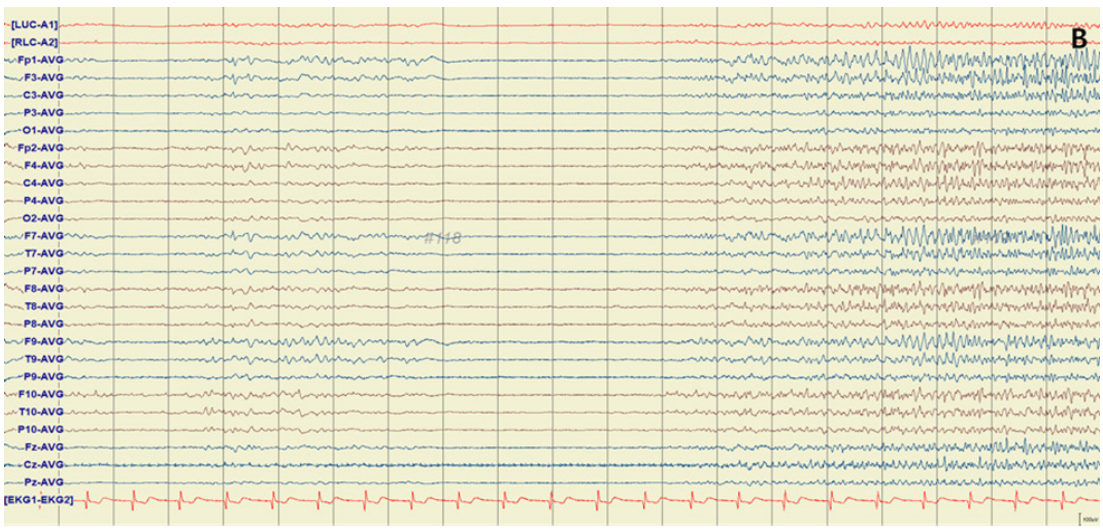
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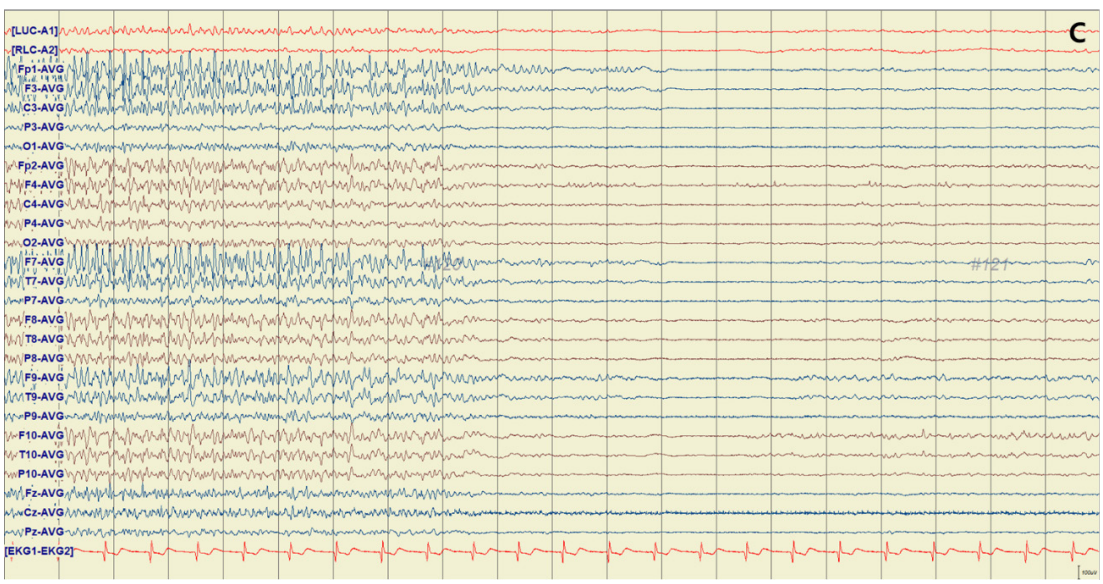
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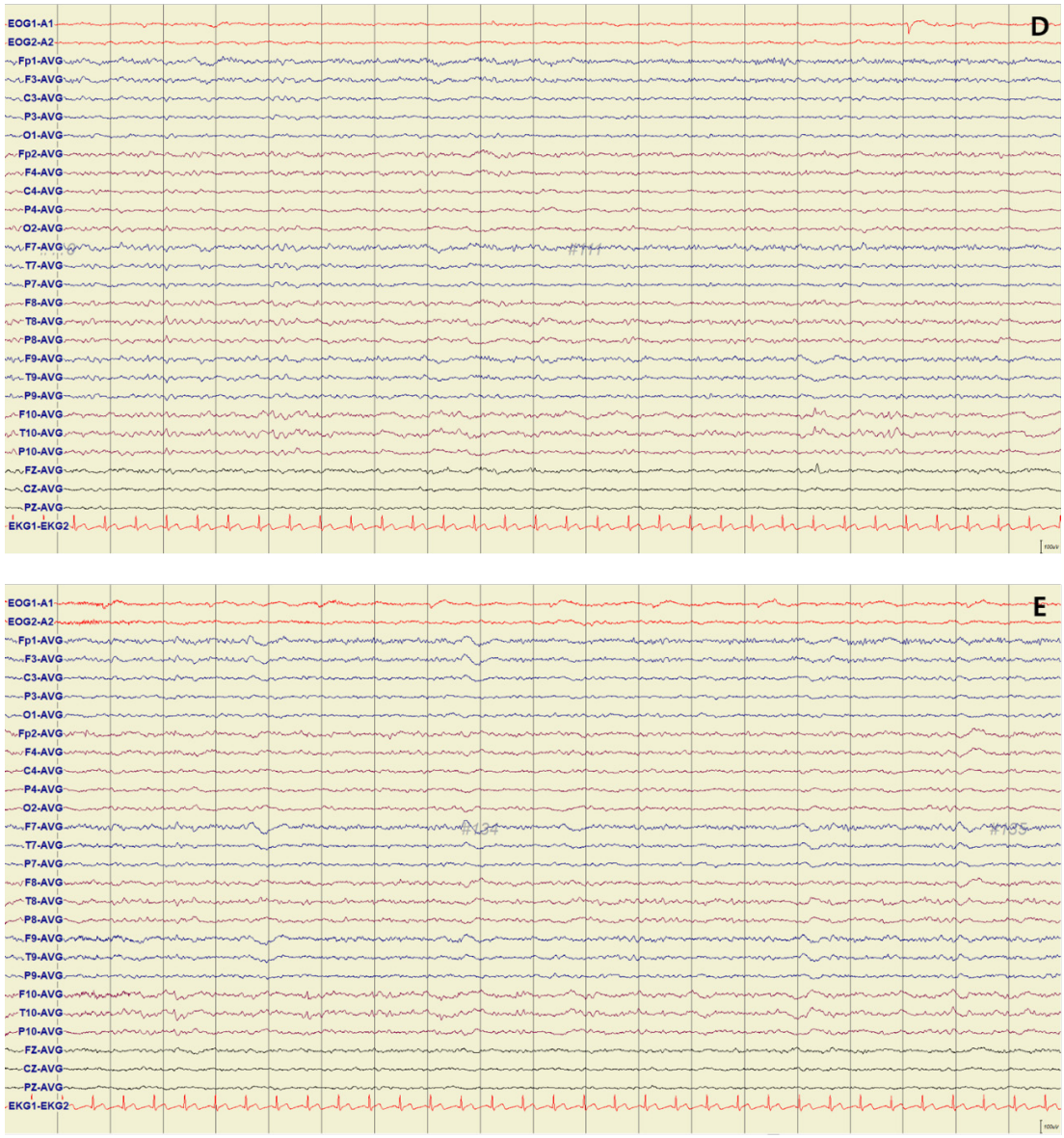

Figure 2. Serial EEG findings of patient during treatment.
EEG taken on the day of admission shows electrographic seizures with repetitive polyspikes that are maximum on the left frontal area (A). EEG taken 1 day after VNS surgery shows still electrographic seizures originating at Fp1 (B, C). EEG taken 4 months after VNS surgery shows nonspecific slow activities without epileptiform discharge (D, E). EEG, electroencephalogram; VNS, vagus nerve stimulation

and various treatment options are being explored beyond drug therapy. A study of 83 patients with DRE who underwent VNS surgery showed that VNS stimulation is effective in reducing the seizure frequency or controlling SE, with half of patients remaining SE-free for at least 2 years after the follow-up.[7] In a systematic review of 26 articles describing 45 patients treated with VNS for SE, acute VNS implantation led to the cessation of RSE/SRSE in 74% of cases.[1] Although further research is needed, such as appropriate stimulation paradigms and implantation timings, VNS has the potential to interrupt RSE and SRSE in many patients.

Although the mechanism by which VNS inhibits seizures is not yet clear, it has been confirmed that VNS increases the concentration of norepinephrine and serotonin, increases gamma-aminobutyric acid, which suppresses seizures and decreases aspartate, which increases seizures.[8,9]

In addition, it is known to reduce excitability by increasing the CBF of both thalamus, thereby suppressing thalamocortical relay neurons, and reducing brain inflammation by decreasing specific cytokines.[10,11] While these mechanisms could be considered potential contributors to SR-NCSE interruption, it has yet to be proven in well-controlled trials.[1]

Because the prognosis of NCSE varies according to the type of NCSE, unlike standardized and rigorous treatment algorithms developed for convulsive SE, there are many different treatment opinions. Therefore, most current recommendations for adult patients with NCSE are based on limited evidence and expert opinions.[12] As there was a high risk of complications and poor outcomes following prolonged admission to the intensive care unit for the treatment of SRSE, VNS was considered as a non-pharmacological treatment. This case report describes the successful treatment of SR-NCSE with VNS. However, as the first improvement in EEG was confirmed 2.5 months after VNS surgery, we cannot conclusively attribute it solely to the effects of VNS. Another limitation is that central nervous system infection or autoimmune encephalitis was not confirmed because the CSF examination was not performed. Nevertheless, VNS can be considered a relatively safe treatment for SR-NCSE in patients who do not show improvement despite receiving the best-recommended treatment. Further prospective studies are warranted to validate the efficacy and safety of VNS in patients with SR-NCSE.

DISCLOSURE

Ethics: The patient provided consent to the study.

Financial support: None.

Conflicts of interest: None.

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