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Clinical letter

Sustained seizure freedom with transcutaneous vagal nerve stimulation in drug-resistant epilepsy caused by subcortical band heterotopias

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1. Introduction

Epilepsy is associated with increased morbidity, mortality, and impaired quality of life. One third of epilepsy patients are drug-resistant. The development of new anticonvulsants has not led to significant improvement in seizure outcomes, emphasizing the need for non-pharmaceutical approaches.

Classic scheduled (invasive) vagus nerve stimulation (iVNS) is a well-established non-pharmaceutical method; however, the invasive nature of the procedure and limitations concerning imaging (MRI) might discourage patients and physicians. Transcutaneous vagus nerve stimulation (tVNS) is based on the stimulation of the auricular branch of the vagus nerve, which innervates the posterior wall of the external auditory meatus and the concha. Projections of this branch to the solitary tract have been shown. Anticonvulsant efficacy was illustrated by the following studies: a pilot study (reduced seizures in 5/7 patients during a 9-month follow-up) [1], a double-blind randomized control trial (significant reduction of seizure frequency in active group; however, difference between seizure reduction and responder rates between active and inactive groups were not significant) [2], and a single-center trial of 20 patients spanning 6 months describing an average seizure reduction but not reaching statistical significance [3]. None of these studies reported long term seizure freedom, but there were few or no side effects and no negative impact on quality of life or cognitive outcome [1–3]. The device is easy to use and well tolerated.

2. Case report

A 24-year-old female patient having seizures since the age of eleven has been treated by us since 2013. She presented with focal to bilateral tonic-clonic seizures with anxiety and dizziness, sometimes with auras, and always with oral automatisms. At first, seizures were sleep-related; later, they also occurred during wakefulness. During the last 12 years, they exclusively occurred during wakefulness. Cerebral MRI revealed bilateral subcortical band heterotopias (Fig. 1), and genetic testing showed a heterozygous mutation in exon 5 of the *DCX* gene. EEG displayed regional slowing in the theta-band in the left and right temporal regions. The patient reported delayed development but ultimately achieved all developmental milestones. She did not suffer from any comorbidities; there was no family history of epilepsy. The patient showed only minor cognitive impairment and achieved nine years of education before starting training as a household assistant.

Upon epilepsy diagnosis, lamotrigine was begun, leading to seizure freedom for 18 months. With seizure recurrence, lamotrigine, levetiracetam, and lacosamide were administered without achieving seizure freedom. At her first visit, she presented with three to four reported seizures per year and suffered from mild side effects from polytherapy (2000 mg levetiracetam, 150 mg lacosamide, 400 mg lamotrigine). Lamotrigine was tapered off without increase in seizure frequency. Treatment was then complicated by increased anxiety concerning attacks, requiring psychotherapy. Due to the anxiety, add-on therapy with pregabalin (300 mg/d) was started, without achieving significant seizure control. In June 2014, she was offered the additional treatment with tVNS. In the first month, one bilateral tonic-clonic seizure occurred after maladherence to anticonvulsant medication; another focal unaware seizure was observed after 10 weeks of stimulation. Since August 2014, the patient has been seizure free.

Stimulation began with 0.8 mA and was adjusted to 1.5 mA. It was performed four hours daily, preferably in the afternoon, and mostly in one session. Stimulation history was excellent, as electronically documented by the device (Fig. 2). Local skin alterations or other clinical signs of side effects were not detected. EEG did not differ from the pre-stimulation registration. Anxiety was last reported 18 months after starting stimulation; psychopathological evaluation was normal thereafter.

Seizure freedom led to psychosocial stabilization; the patient is now working as a household assistant and has acquired a driver's license.

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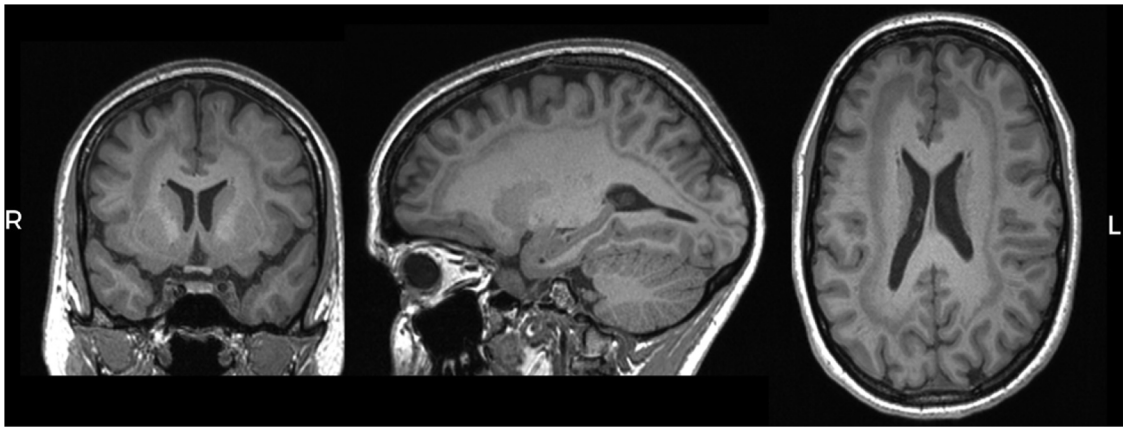

Fig. 1. 3D-T1-MPRAGE of the index patient in coronal, sagittal, and axial orientations. Extensive bi-hemispheric lesion.

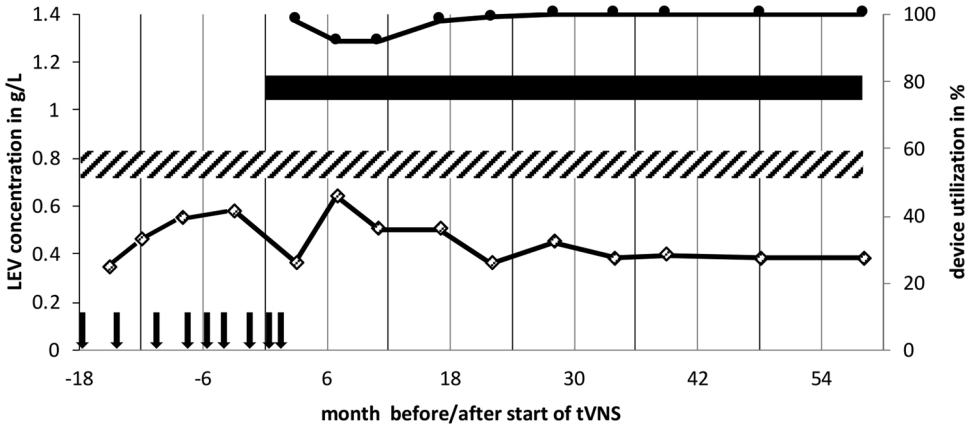

Fig. 2. Seizure (arrow), anticonvulsant medication (striped bar), serum concentration of levetiracetam (square), transcutaneous vagus nerve stimulation (black bar), utilization of the tVNS in the previous 3 month as documented electronically by the device (spots).

3. Discussion

Our patient had insufficient seizure control with infrequently occurring but disabling focal to bilateral tonic-clonic seizures. As epilepsy surgery was not feasible, tVNS was performed to attempt to improve seizure control. Unexpectedly, the patient reported sustained seizure freedom for a period of 56 months at last follow-up. Quality of life, as assessed by the patient, her family, and the treating physicians, increased dramatically. This result does not prove that this impressive clinical success is solely caused by regular tVNS. Pausing tVNS, however, was not an acceptable option, for ethical reasons. The long history of unsuccessful drug treatment, however, does support attributing seizure remittance to tVNS and not to a spontaneous change in the course of epilepsy.

The reported case underscores the idea of alternative approaches as an add-on to regular pharmaceutical treatment. Long-term data on neurostimulation suggest increasing efficacy in patients with drug-resistant epilepsy; even in patients who do not immediately benefit from treatment, patience appears worthwhile [4]. As the tVNS device is easy to use and non-harmful, with rare side effects, treatment could be attempted in many patients. For longer utilization, however, the necessity of spending four hours using the device may become annoying and negatively influence adherence. Therefore, studies on the transferability of tVNS results to iVNS results would be helpful in selecting patients who may benefit from iVNS by first examining effects of vagus nerve stimulation using noninvasive methods.

4. Conclusion

Transcutaneous vagus nerve stimulation is an easy-to-use non-pharmaceutical treatment. We report an astonishing and sustained success in the treatment of a case of drug-resistant epilepsy, suggesting that tVNS is an alternative regimen in non-seizure-free patients.

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