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Transcutaneous Auricular Vagus Nerve Stimulation Therapy in Patients with Cognitively Preserved Structural Focal Epilepsy: A Case Series Report

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Key words: Transcutaneous Auricular Vagus Nerve Stimulation, taVNS, VNS, epilepsy, cognitive function

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Summary

Objective: Transcutaneous auricular vagus nerve stimulation (taVNS) was performed in two patients suffering structural focal epilepsy with preserved intellectual ability to show the feasibility of taVNS for specific patient groups.

Case Presentations: Patient 1 was a 24-year-old woman with frontal lobe epilepsy who had weekly hyperkinetic seizures despite multiple anti-seizure medications. Patient 2 was a 27-year-old woman with parietal lobe epilepsy and focal cortical dysplasia in the vicinity of the lipoma in the corpus callosum. She experienced weekly focal-impaired awareness seizures even with anti-seizure medication. taVNS was applied to the left earlobe of both patients at 1.5 mA, 25 Hz, 250 μs pulse width, and 30 s stimulation with 30 s rest for 4 hours per day. Over an 8-week baseline and 20 weeks of stimulation, the rate of reduction in seizure frequency was evaluated, along with quality-of-life using the Short-Form 36-Item Health survey.

Results: At baseline, we measured up to 11 and 12 focal seizures per week in Patient 1 and 2, respectively, with both patients achieving seizure freedom after 4 and 20 weeks taVNS, respectively. Patient 1 and 2 were observed for 18 and 14 months, respectively, including the clinical trial and follow-up observation period. Quality-of-life ratings increased in both patients, and no significant adverse events occurred during the study period. During the maintenance period after 20 weeks, seizures remained absent in Patient 1, and seizures remained reduced in Patient 2.

Conclusion: Our results demonstrate that taVNS may be a promising tool for structural focal epilepsy with preserved cognitive function. A multicenter double-blind clinical trial is needed to confirm the role of taVNS as an anti-seizure tool.

1. Introduction

Vagus nerve stimulation (VNS) produces significant efficacy for epileptic seizures in some patients, with 22.5% of patients from a study of 400 patients aged 1-76 years experiencing seizure reductions of 90% or greater [1]. Furthermore, Sourbron et al. [2] compared children with and without intellectual disability who received VNS and found that VNS was more effective in those who remained intellectually intact, while Katagiri et al. [3] also reported that VNS was more effective for patients in whom speech was preserved compared with those in whom speech was absent.

Transcutaneous auricular VNS (taVNS), which does not require surgical intervention, is a potential treatment for suppressing epileptic seizures via electrically stimulating the auricular branch of the vagus nerve [4]. A multicenter, double-blind study of taVNS in patients with epilepsy by Bauer et al. in 2016 [5] reported a comparison between a 25 Hz stimulation group of 39 patients and an active control group of 37 patients with 1 Hz stimulation. They demonstrated a significant 34.2% reduction in seizure frequency in patients in the 25 Hz group who completed the full 20-week treatment. However, they could not prove non-inferiority between taVNS and conventional VNS, because VNS can reduce seizures by approximately 55.8% in all test patients [1, 6].

These taVNS studies have applied to all types of epilepsies, but the results have not been compared in terms of structural focal epilepsy and cognitive dysfunction. Herein, we present two cases of taVNS in patients with structural focal epilepsy with preserved intellectual function to assess the feasibility of this treatment for specific patients.

2. Patients and Methods

2.1. Patient selection criteria

We selected our patients using the following selection criteria: i) patient with structural focal epilepsy, ii) inoperable patient because of multiple or undetermined epileptogenic foci, and iii) preserved cognitive function.

We performed taVNS therapy only in these two patients, because we only had two taVN stimulators.

2.2. Intervention

A taVN stimulator (Soterix Medical, Inc.) was used with stimulation parameters and the site of stimulation defined according to previously described methods [5]. Stimulation was performed with an electrode attached to the left earlobe. The stimulation current was 1.5 mA, at 25 Hz, pulse width of 250 μs, 30 s stimulation and 30 s rest for 4 h per day. The duty cycle of taVNS was 2 h per 24 h (8.3%) which was similar to the initial setting of conventional VNS at 30 s per 330 s (9.0%). Stimulation could be interrupted, but the total stimulation time was still 4 h per day.

2.3. Evaluation methods

Baseline evaluation was conducted for 8 weeks, followed by a 20-week evaluation after the start of stimulation. The evaluation was based on the change in seizure frequency of focal seizures (focal awareness seizures [FAS], focal impaired awareness seizures [FIAS], and focal to bilateral tonic clonic seizures) per week. These evaluation methods followed the study methods of Bauer et al. [5].

The Short-Form 36-Item Health survey (SF-36) also assessed quality-of-life before

the start of stimulation and at the end of the 20-week stimulation period. In addition, the occurrence of side effects was checked during monthly visits, and any adverse events were reported by phone and evaluated during the period of the study.

The total observation period for Patient 1 and 2 was 18 and 14 months, respectively, including the clinical trial and a follow-up observation period.

2.4. Ethics

This study was evaluated and approved by the Clinical Research Review Committee of Hokkaido University Hospital (jRCTs012210049). Written consent was obtained for the study.

3. Case presentations

3.1. Patient 1

Patient 1 was a 24-year-old woman with seizure onset at 6 years of age. She had seizures that occurred in clusters, especially at night, clustering every few minutes. Her seizures were described as hyperkinetic seizures with eye deviation and head-turning to the left. Soon after the eye and head movement, hyperkinetic movement in the upper and lower limbs without synchronous rhythm occurred. Her ictal EEG showed diffuse low amplitude beta waves over bilateral hemispheres, building up to high amplitude, left hemispheric dominant, sharply contoured slow waves, obscured by muscle artifacts. (Fig. 1A). Her interictal EEG showed frequent, diffuse, high amplitude, sharply contoured, spiky notched theta and delta waves over the bilateral frontal, central, parietal, and midline regions during wakefulness (Fig. 1B) and sleep. Her MRI showed no abnormal findings (Fig. 2 top right). Her seizures were diagnosed as hyperkinetic

seizures originating from the frontal lobe and she was diagnosed with cryptogenic structural frontal-lobe epilepsy.

She graduated from a normal high school and works in general employment. Her full-scale IQ was 114 using the Wechsler Adult Intelligence Scale (WAIS) - Fourth Edition. Genetic testing was not done.

Her anti-seizure medication included carbamazepine (max 300 mg/day), topiramate (max 200 mg/day), clobazam (10 mg/day), lamotrigine (max 550 mg/day), perampanel (max 12 mg/day), zonisamide (max 300 mg/day), and lacosamide (max 200 mg/day), but no seizure control was obtained. Medication during the study period was unchanged with carbamazepine (300 mg/day), lamotrigine (550 mg/day), perampanel (12 mg/day), zonisamide (300 mg/day), and lacosamide (200 mg/day) (Fig. 2 top).

She had 5-10 FIAS per week at baseline, but her seizures resolved after 4 weeks of stimulation (Fig. 2 top). Quality-of-life ratings by SF-36 totaled 517.6 at baseline and 630.8 at 20 weeks. Only body pain decreased from 100 to 62, while the rest of the scores were unchanged or increased to a perfect score (Fig. 3 top). The average stimulation time during the study period was 4.0 h; no severe adverse events were observed.

After the 20-week study period, the patient kept on using taVNS stimulation without any seizure recurrence. It was possible to reduce her lamotrigine dose starting at 27 weeks in the maintenance period (Fig. 2 top). Her interictal EEG after 44 weeks of taVNS stimulation showed rare, diffuse, high amplitude, sharply contoured, spiky notched delta waves over the bilateral frontal, central, parietal, and midline regions during sleep (Fig. 1C). There were no abnormal EEG findings during wakefulness.

3.2 Patient 2

Patient 2 was a 27-year-old woman with seizure onset at 14 years of age. Her seizures were described as FAS which occurred 2-6 times a week with numbness in both upper extremities predominantly in both palms. During the FAS her palms were always sweaty. The FAS evolved to FIAS which occurred 2-10 times per week with flexor tonic extension of both upper extremities and eye opening for 10 s. FAS sometimes occurred repeatedly every 1-2 min for 2-3 h, especially during menstruation and singing or shouting at her favorite singer's concerts. Her MRI showed the presence of the lipoma in the corpus callosum and surrounding focal cortical dysplasia (FCD) (Fig. 2 lower right). She could not undergo lesionectomy of FCD because the location was wide, and we could not define the extent of resection. Her interictal EEG showed abundant right hemispheric dominant, diffuse, high amplitude, sharply contoured theta and delta waves over the bilateral frontal, central, and midline regions during wakefulness and sleep (Fig. 1D). Thus, MRI and EEG findings suggested a possible epileptogenic focus in the FCD in the vicinity of the lipoma in the corpus callosum (Fig. 2 bottom right).

She graduated from a university engineering department and is employed in the public sector. Her full-scale IQ was 114 using the WAIS-Fourth Edition. Genetic testing was not done.

Carbamazepine (max 700 mg/day), lacosamide (max 100 mg/day), lamotrigine (max 100 mg/day), and levetiracetam (max 2500 mg/day) were used, but no seizure control was obtained. The medications administered during the study period were unchanged with carbamazepine (700 mg/day) and levetiracetam (2500 mg/day) (Fig. 2 bottom).

She had 1-12 focal seizures per week at baseline, but the seizures ceased by 20 weeks. She also had 0-10 FIAS per week at baseline, which ceased at 17 weeks (Fig. 2

bottom). Her SF-36 assessment of quality-of-life totaled 604.5 at baseline but was 628.3 at 20 weeks (Fig. 3 bottom). Only vitality decreased from 62.5 to 56.3, but other categories remained unchanged or increased to a perfect score. The average stimulation time during the study period was 4.0 h; no severe adverse events were observed.

After the 20-week study period, she has continued using taVNS stimulation without any change in seizure frequency or duration (Fig. 2 bottom). Her seizure reduction rate was 86%. Her interictal EEG after 44 weeks of taVNS stimulation showed occasional right hemispheric dominant, diffuse, high amplitude, sharply contoured theta and delta waves over the bilateral frontal, central, and midline regions during sleep. There was no abnormal EEG finding during wakefulness (Fig. 1E).

4. Discussion

Several studies of taVNS have been reported in other facilities, but none with such satisfactory results as our current case series. The only multicenter, double-blind study conducted failed to demonstrate superiority of taVNS to VNS and was not applied clinically [5]. They demonstrated a significant 34.2% reduction in seizure frequency in patients in the 25 Hz group who completed the full 20-week treatment (n = 26, p = 0.034). In addition, complete seizure freedom during the last 28 days of the study appeared in 3 of 39 patients in the 1 Hz group and in 1 of 37 patients in the 25 Hz group. However, they could not prove superiority of 25 Hz taVNS over 1 Hz taVNS because the mean seizure reduction in the last 28 days of the treatment was –2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p = 0.146). But the conclusion they have drawn may need to be reconsidered based on our results. They used different stimulation parameters to our clinical study and while they mainly focused on

stimulation frequencies (1 and 25 Hz), they used the same stimulation pulse width of 250 μs for both frequencies. In our clinical experience, one of the most important factors that reduces the electric battery storage is the duration of stimulation. Although they used only 1 Hz stimulation as control, the stimulation might be partially effective in preventing seizures when used at a pulse width of 250 μs. If they used 1 Hz stimulation at 20 μs, for example, as the control stimulation, they might have achieved significant differences in their clinical trial.

In comparison, conventional VNS, in which electrodes are implanted in the cervical vagus nerve trunk, can reduce seizures by approximately 55.8% for all test patients [1, 6]. These studies did not specify which patients were eligible and was indicated for all epilepsy patients [5]. taVNS impulses initially reach the nucleus of the solitary tract and activate the locus-coeruleus-norepinephrine system [7]. However, the effects of taVNS are particularly seen in the thalamus, which also has a high influence on cognitive function. This mechanism is almost similar to that of conventional VNS which affects the ventro-posterior medial nucleus of the thalamus [8, 9]. A fMRI study also demonstrated activation by VNS mainly occurs in the frontal and occipital lobes and the thalamus in effective patients [10]. Another fMRI study showed a change in the functional connectivity between the thalamus and precentral gyrus in epilepsy patients following VNS [11]. An animal study has also demonstrated intense labelling occurs in the habenular nucleus of the thalamus after VNS, using the nuclear protein, Fos, that is expressed under conditions of high neural activity [12]. Deep brain stimulation (DBS) therapy for epileptic patients has provided evidence that the main target locations in the thalamus for preventing seizures are the anterior thalamic nuclei [13]. VNS also stimulates the anterior thalamic nuclei and demonstrates an anti-seizure effect, like DBS

[10]. Functional recovery of anterior thalamic nuclei lesions is also related to recovery of cognitive dysfunction in an animal model [14]. The thalamus engages in sensory processing, attention, decision-making and memory [15]. We speculate that cognitive function is strongly influenced by thalamic function and the effect of VNS, taVNS, and DBS occurs because neuromodulation in the brain is regulated by thalamic function. In the initial DBS study, the patients were selected after evaluation of cognitive function with an IQ of more than 70 [13]. We selected our patients according to the above consideration and chose cognitively preserved patients whose thalamic function was also preserved, as good candidates for treatment by taVNS. Therefore, we hypothesize that VNS, particularly taVNS, may be effective in patients with residual cognitive brain function.

In the Bauer et al. study, the stimulation setting used for the control patients in the double-blind study consisted of 1 Hz, 250 μs pulse for 30 s followed by 30 s rest for a total of 4 h [5]. However, considering the effects in this study, this may not be a suitable sham stimulation for the control group and may have had some epileptic suppressive effects. A double-blind study will be necessary to evaluate the effects of taVNS in the future, but the method of stimulation of the target patient should be considered.

Quality-of-life assessment using SF-36 showed an increase in total scores at 20 weeks compared to baseline in both patients. The decrease in body pain rating in Patient 1 was thought to represent an increase in discomfort due to the taVNS.

In conclusion, taVNS is a noninvasive treatment that does not require surgery and may be considered as a new option for the treatment of epilepsy, particularly in patients with structural focal epilepsy and preserved cognitive function.

Consent for Publication

We have obtained consent from the patients' parents or guardians to publish this case series as it includes detailed medical histories of the patients that may identify them.

Author Contributions

HS and MM were responsible for the organization and coordination of the study. KE, MN, YU, SN, MN, SK, TG, YH, and HS treated the patients as attending physicians and obtained clinical data. KM and MM developed the trial design.

All authors contributed to the writing of the final manuscript. All members of the study team contributed to the management or administration of the trial.

Disclosure of Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was evaluated and approved by the Clinical Research Review Committee of Hokkaido University Hospital (jRCTs012210049). Written consent was obtained for the study.

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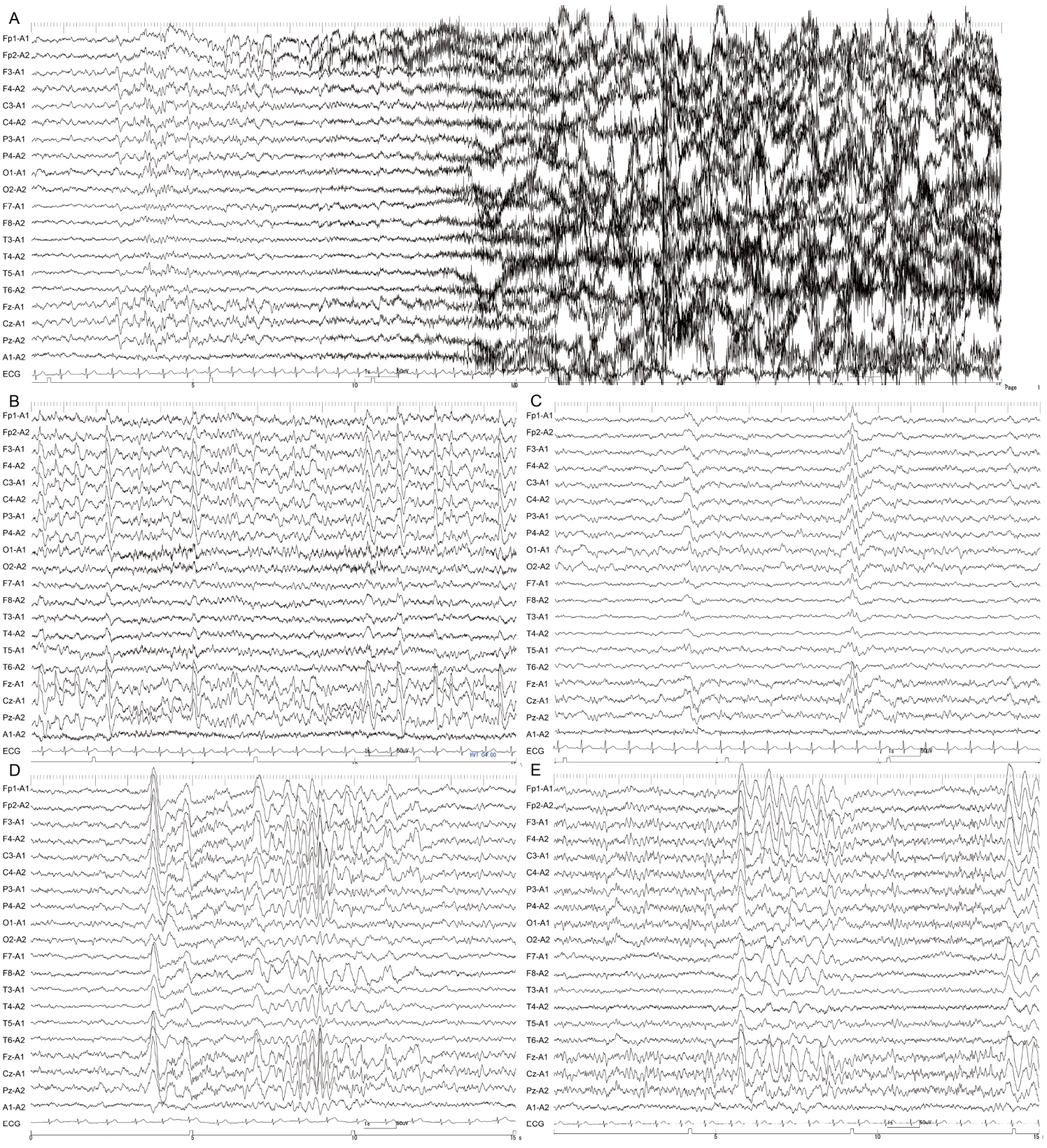
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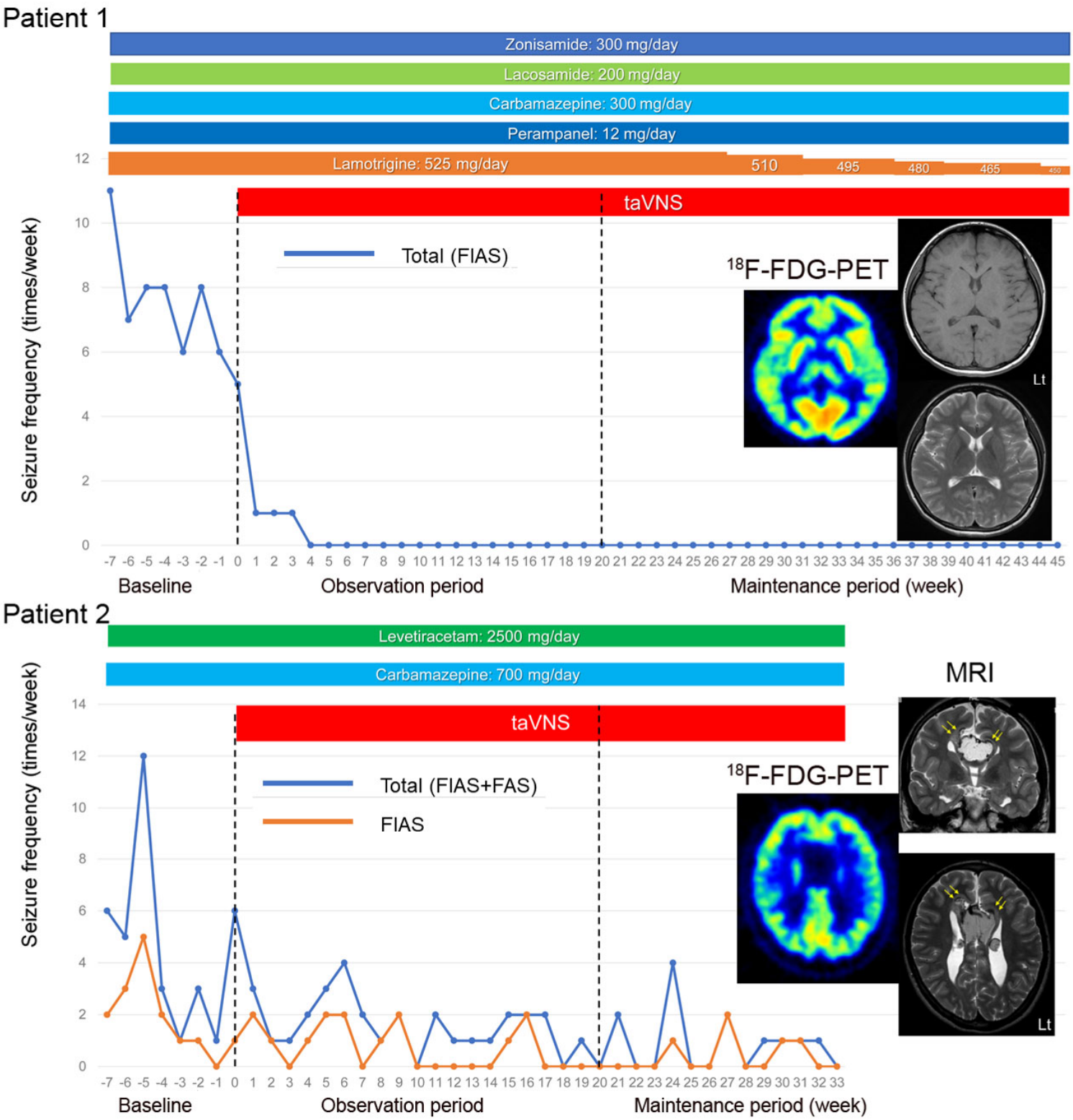
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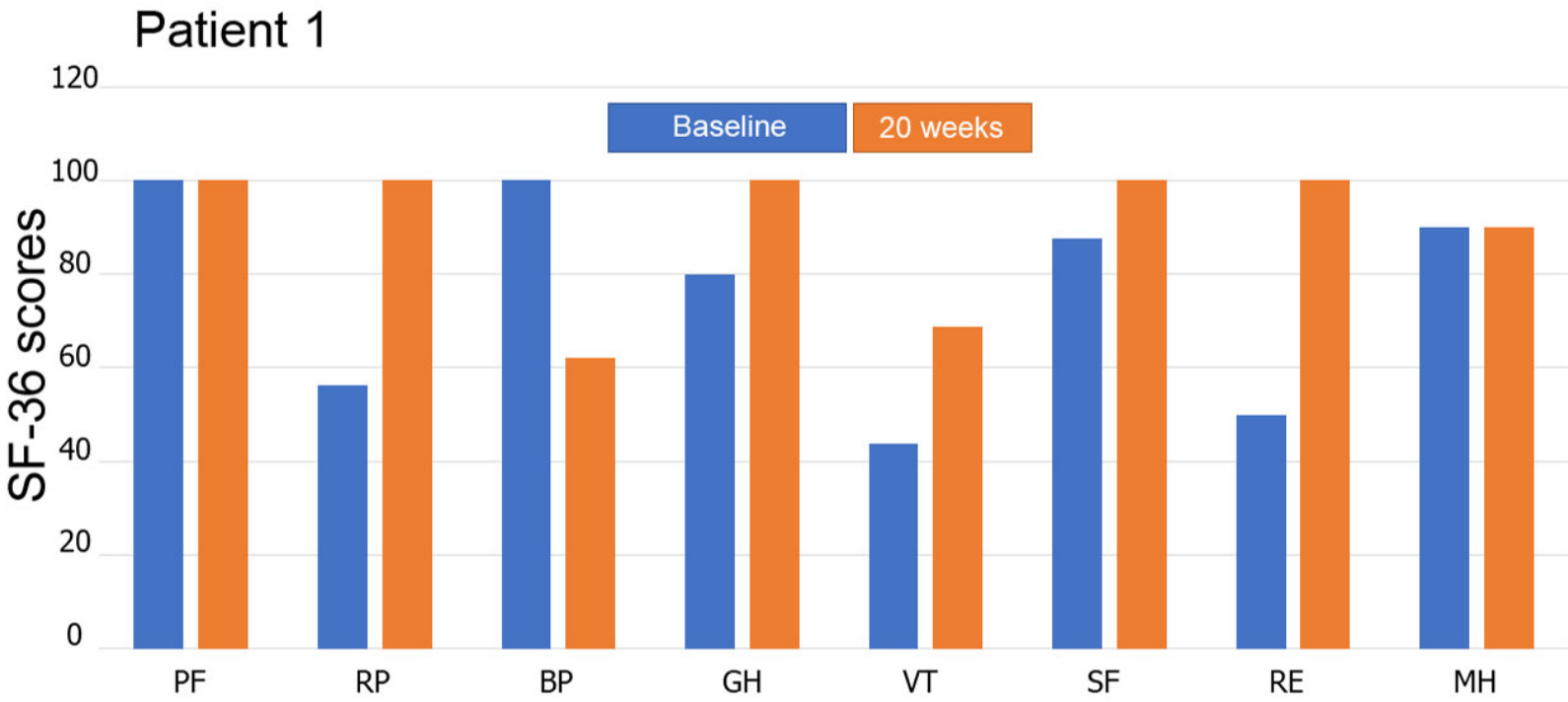
Fig. 1. EEG findings in Patients 1 and 2. (A) Ictal discharges of Patient 1 showed diffuse, low amplitude beta waves over bilateral hemispheres, building up to high amplitude, left hemispheric dominant, sharply contoured slow waves, obscured by muscle artifacts (time constant, 0.3 s; high frequency filter, 120 Hz; notch filter, 50 Hz). (B) Interictal epileptic discharges before transcutaneous auricular vagus nerve stimulation (taVNS) in Patient 1. Her interictal EEG showed frequent diffuse, high amplitude, sharply contoured, spiky notched theta and delta waves over the bilateral frontal, central, parietal, and midline regions during wakefulness (time constant, 0.3 s; high frequency filter, 120 Hz; notch filter, 50 Hz). (C) Interictal epileptic discharges after taVNS in Patient 1. Her interictal EEG after 44 weeks of taVNS stimulation showed rare diffuse, high amplitude, sharply contoured, spiky notched delta waves over the bilateral frontal, central, parietal, and midline regions during sleep (time constant, 0.3 s; high frequency filter, 120 Hz; notch filter, 50 Hz). (D) Interictal epileptic discharges before taVNS in Patient 2. Her interictal EEG showed abundant right hemispheric dominant, diffuse, high amplitude, sharply contoured theta and delta waves over the bilateral frontal, central, and midline regions during wakefulness and sleep (time constant, 0.3 s; high frequency filter, 120 Hz; notch filter, 50 Hz). (E) Interictal epileptic discharges after taVNS in Patient 2. Her interictal EEG after 44 weeks of taVNS stimulation showed occasional right hemispheric dominant, diffuse, high amplitude, sharply contoured theta and delta waves over the bilateral frontal, central, and midline regions during sleep (time constant, 0.3 s; high frequency filter, 120 Hz; notch filter, 50 Hz). There was no abnormal EEG finding while she was awake.

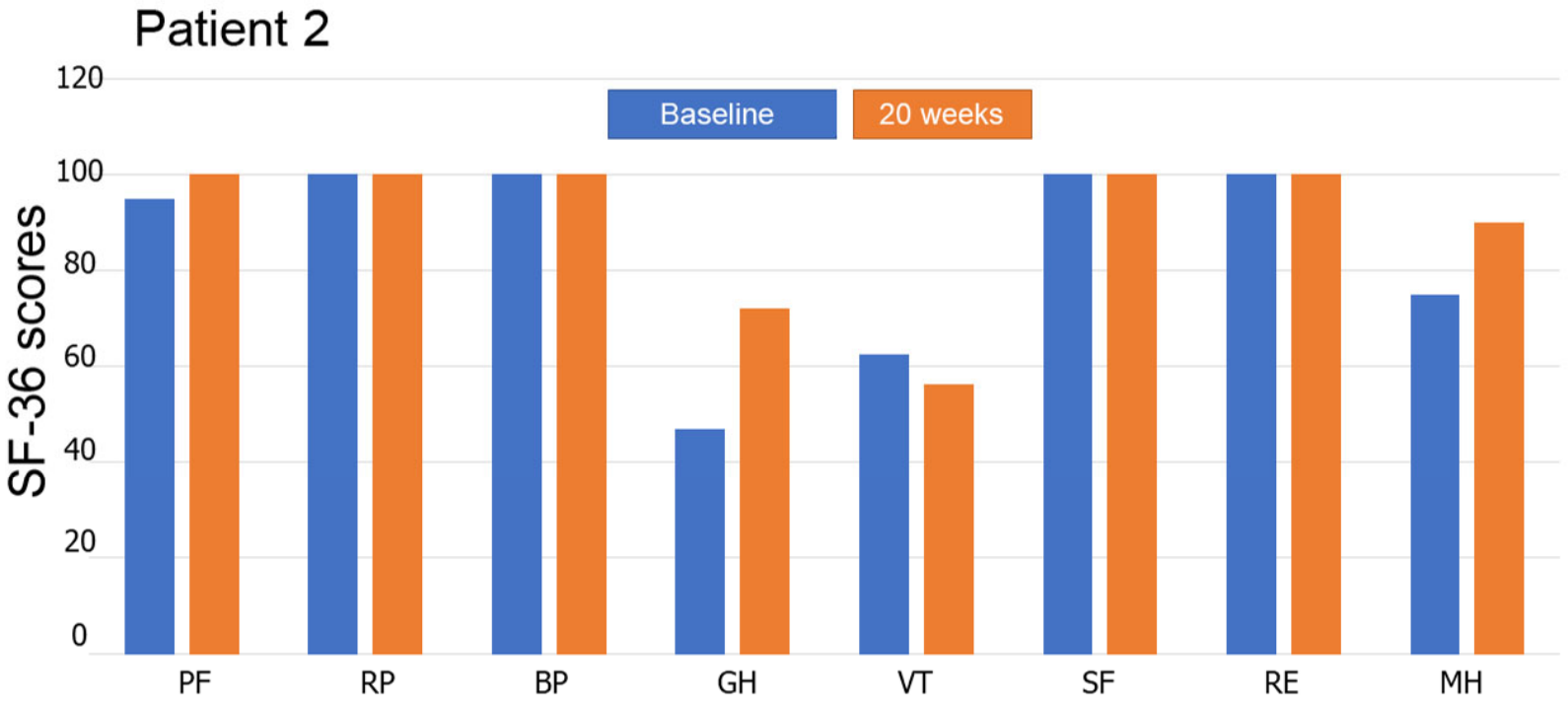
Fig. 2. Time course of seizure frequency, medication, and transcutaneous auricular vagus nerve stimulation (taVNS). (Top panel) The seizures in Patient 1 were focal impaired aware seizures (FIAS) only. These seizures disappeared 4 weeks after starting taVNS, and seizure suppression continued past the 20-week evaluation period. Seizures remained resolved and this continued during the maintenance period after 20 weeks, and it was possible to reduce the lamotrigine dose at 27 weeks in the maintenance period. (Top right) Her MRI and 18F-fluorodeoxyglucose positron emission tomography (PET) showed no abnormal findings. (Bottom panel) Patient 2 had mixed FIAS and focal awareness seizures (FAS), with the total number of seizures decreasing markedly around 7 weeks after starting taVNS and resolving after 20 weeks of taVNS, while FIAS markedly decreased at 10 weeks after stimulation and resolved at 17 weeks. Seizures remained reduced and this continued during the maintenance period after 20 weeks. (Bottom right) MRI showed the presence of a lipoma in the corpus callosum and surrounding focal cortical dysplasia (yellow arrows). 18F-PET showed hypometabolism at the focal cortical dysplasia.

Figure 3. Quality-of-life evaluation in each patient. Bars indicate the clinical value of the Short-Form 36-Item Health survey (SF-36) scores at baseline (blue) and after 20 weeks transcutaneous auricular vagus nerve stimulation (orange). (Top panel) In Patient 1, only body pain (BP) decreased, while the other quality-of-life measures either improved or remained unchanged. (Bottom panel) In Patient 2, only vitality (VT) decreased slightly, and the remaining scores either improved or remained unchanged. PF, physical functioning; RP, role limitation due to physical problems; GH, general health perception; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health.


A
B
C
D
E
Fp1-A1
Fp2-A2
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2
O1-A1
O2-A2
F7-A1
F8-A2
T3-A1
T4-A2
T5-A1
T6-A2
Fz-A1
Cz-A1
Pz-A2
A1-A2
ECG
1s
50uV
HV 04:00
Page 1


Patient 1
Zonisamide: 300 mg/day
Lacosamide: 200 mg/day
Carbamazepine: 300 mg/day
Perampanel: 12 mg/day
Lamotrigine: 525 mg/day
510
495
480
465
taVNS
Total (FIAS)
18F-FDG-PET
Lt
Seizure frequency (times/week)
Baseline
Observation period
Maintenance period (week)
Patient 2
Levetiracetam: 2500 mg/day
Carbamazepine: 700 mg/day
taVNS
Total (FIAS+FAS)
FIAS
MRI
18F-FDG-PET
Lt
Seizure frequency (times/week)
Baseline
Observation period
Maintenance period (week)


Patient 1
Baseline
20 weeks
SF-36 scores
120
100
80
60
40
20
0
PF
RP
BP
GH
VT
SF
RE
MH


Patient 2
Baseline
20 weeks
SF-36 scores
120
100
80
60
40
20
0
PF
RP
BP
GH
VT
SF
RE
MH