Epilepsy Research 140 (2018) 66–71

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Insufficient efficacy of vagus nerve stimulation for epileptic spasms and tonic spasms in children with refractory epilepsy

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A R T I C L E I N F O

Keywords:
Vagus nerve stimulation
Efficacy
Epileptic spasms
Tonic spasms
Refractory epilepsy
Children

A B S T R A C T

Background: Vagus nerve stimulation (VNS) leads to palliation of refractory seizures. Epileptic spasms (ES) and tonic spasms (TS) appear in children with West syndrome and symptomatic generalized epilepsy. Both types of spasms are often characterized by truncal muscular contractions and ictal electroencephalography (EEG) findings comprising the contiguous phases: phase 1) 15–20 Hz, spindle-like fast activity (occur in 70%), 2) diffuse polyphasic δ/θ waves (100%), and 3) electrodecremental activity (70%). Here, we examined the effect of VNS on these spasms that are uniformly associated with the EEG and electromyogram changes.
Methods: A consecutive series of 32 patients satisfied the inclusion criteria consisting of 1) medically refractory epilepsy, 2) VNS implantation between 2010 and 2015, 3) implantation of VNS before the age of 20 years, and 4) follow-up > 2 years. From this cohort, 16 patients had spasms (ES/TS group), whereas the remaining 16 had partial seizures with or without secondary generalization (PS/SG group). We compared seizure outcomes between the two groups, and also determined the factors predicting these outcomes within the ES/TS group.
Results: The outcomes after 2 years of implantation, defined using the McHugh classification, were as follows: II (for 2 patients), III (5), and V (9) in the ES/TS group; and I (3 patients), II (6), III (2), IV (1), and V (4) in the PS/SG group. The ES/TS group had significantly worse outcomes than the PS/SG group (p = 0.024, Mann-Whitney U test). Multivariate ordinal logistic regression analysis revealed that shorter mean durations of ictal events were associated with better seizure outcomes following VNS implantation (p = 0.007).
Significance: Only 13% of the patients in the ES/TS group had seizure reductions of greater than 50%. VNS was less effective for the treatment of patients with ES/TS than for those with PS/SG and those described in previous studies.

1. Introduction

1.1. Vagus nerve stimulation and seizure types

Vagus nerve stimulation (VNS) leads to palliation of refractory seizures. VNS affects the nucleus of the solitary tract and the locus coeruleus in the brainstem (Henry, 2002; Kotagal, 2011). VNS has neuromodulatory effects on the cerebral cortices and subcortices by increasing the transmission of serotonin and noradrenaline (Shiramatsu et al., 2016; Kotagal, 2011).

The clinical indication for VNS is partial seizures (PS) in the United States, and PS and generalized seizures in other countries. In a meta-analysis of the efficacy of VNS, seizure frequency was reduced by an average of 45%. There was a 36% reduction in seizure frequency 3–12 months after implantation and a 51% reduction 12 months following the procedure (Englot et al., 2011). In a large study of VNS therapy in children, reduction rates ≥50% 6, 12, and 24 months after implantation were found in 32.5%, 37.6%, and 43.8%, of the patients, respectively (Orosz et al., 2014). VNS was less efficacious for the treatment of Dravet syndrome, Lennox-Gastaut syndrome (LGS), and generalized tonic-clonic seizures (GTCS) (Orosz et al., 2014).

Abbreviations: AE, Danti-epileptic drug; CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; ES, epileptic spasms; GABA, gamma-aminobutyric acid; GTCS, generalized tonic-clonic seizures; LGS, Lennox-Gastaut syndrome; TS, tonic spasms; PS, partial seizure; SG, secondary generalization; SGE, symptomatic generalized epilepsy; vEEG, video-EEG; VNS, vagus nerve stimulation

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https://doi.org/10.1016/j.eplepsyres.2017.12.010
Received 29 September 2017; Received in revised form 27 November 2017; Accepted 11 December 2017
Available online 15 December 2017

1.2. Epileptic spasms and tonic spasms

Epileptic spasms (ES) are seizures leading to muscular contraction and appear mainly in patients with West syndrome. Tonic spasms (TS), which are also called brief tonic seizures or tonic-axial seizures, are seizures with longer muscular contractions than ES and appear mainly in patients with symptomatic generalized epilepsy (SGE). The patterns of electroencephalography (EEG) and electromyography (EMG) activity observed in these spasms are comparable (Yamatogi and Ohtahara, 1981). Ictal EEG findings in these patients comprise three contiguous phases: 1) 15–20 Hz spindle-like fast activity in posterior areas, 2) diffuse polyphasic δ/θ waves, and 3) electrodecremental activity (Fusco and Vigevano, 1993; Watanabe et al., 2001). Diffuse polyphasic δ/θ waves occur in 100% and electrodecremental activity occurs in 70% of patients with epileptic spasms (Watanabe et al., 2001). Ictal EMG findings in these patients have rhombus or diamond shapes.

VNS has been used not only for PS or generalized seizures, but also for other types of seizures, including ES and TS. However, in representative previous studies on VNS efficacy for the treatment of seizures, ES, TS, and other seizures leading to falling were generally categorized as drop attacks or atonic seizures (Englot et al., 2011; Lancman et al., 2013). One of the reasons for avoiding the terms ES and TS is thought to be that ictal scalp video-EEG (vEEG) is necessary for the confirmation of these seizures. There has been no study of the effects of VNS on “core” ES/TS confirmed with ictal scalp vEEG.

1.3. Hypothesis and purpose of this study

We hypothesized that VNS is less effective for the treatment of ES/TS confirmed using ictal scalp vEEG than for other types of seizures. In this study, we used patients with partial seizures as the control group and compared the efficacy of VNS in the control group to that for patients with ES/TS.

2. Methods

2.1. Patients

This study was approved by the ethical board of Seirei-Hamamatsu General Hospital. The patient inclusion criteria were 1) developing medically refractory epilepsy, 2) VNS implantation between January 2010 and December 2015, 3) implantation of VNS before the age of 20 years, and 4) follow-up of > 2 year. We initially included 58 patients in the study. We excluded 6 patients without vEEG monitoring records, 4 patients with neurodegenerative disease, 3 patients without sufficient follow-up on their medical records, 2 patients with main seizures of primary generalized tonic-clonic type, 1 patient who died, and 1 patient who was unable to continue VNS due to an infection.

We classified the remaining 41 patients as 23 patients with main seizures of ES/TS type and 18 patients with main seizures of PS or secondary generalized seizure (PS/SG) type based on descriptions on their medical records at the time of VNS implantation. Of the 23 patients with ES/TS, we excluded 5 patients without ictal vEEG records and 2 patients without diffuse polyphasic δ/θ waves at the start of the seizures. Of the 18 patients with PS/SG, we excluded 1 patient without ictal vEEG records and 1 patient who was diagnosed with Rasmussen encephalitis after implantation. Our study thus included 16 patients in the ES/TS group and 16 patients in the PS/SG group. They underwent VNS implantations between December 2010 and May 2015.

2.2. Clinical information

We reviewed the number of antiepileptic drugs (AEDs) used before the implantation, development (severe [intelligence or developmental quotients < 30], moderate [> 31 and < 70], or normal [> 71]) at the time of implantation, age at epilepsy onset and at the time of implantation, time between epilepsy onset and implantation, follow-up period, and maximum VNS current. We evaluated seizure outcomes using data on seizure frequency during the 3 months before VNS implantation and after 1 and 2 years of implantation. We used the McHugh classification outcome scale. This classification system includes 5 levels: class I (80–100% seizure reduction), II (50–79% reduction), III (< 50% reduction), IV (magnet benefit only), and V (no benefit).

2.3. Vagus nerve stimulation

All of the patients were treated using the 105 Aspire HC (VNS Therapy® System; Cyberonics, Inc.; Houston, TX, USA) VNS generator. The implantations were performed at Seirei Hamamatsu General Hospital. Physicians with training in VNS settings managed the current and pulse frequency of the VNS device at Seirei-Hamamatsu General Hospital or at Seirei-Yokohama General Hospital. The current (0.25 mA at once) or duty cycle (< 10% at once) increased at each monthly visit until sufficient seizure reduction was achieved as possible.

2.4. Scalp vEEG

We recorded scalp vEEG (NicoletOne or BMSI6000; Natus Medical Incorporated; Madison, WI) using 19 scalp electrodes placed according to the International 10–20 system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz). For recordings from patients with ES/TS, we also placed electrodes on the patient’s bilateral shoulders. The sampling rates used were 400 Hz and 1024 Hz. We recorded for 16–110 h (mean: 38.5 h) during each monitoring session. We used montages of average referential derivation, AP-bipolar, references of Fz, Cz or Pz, appropriately. We visually analyzed all the ictal EEG records using a time scale of 10 mm/second. The band-pass filter was mainly set to 0.5–60 Hz. Two-hundred and seventy seizures were available for analysis in this study. The EMG electrodes were placed on the patients’ bilateral deltoid muscles.

We reviewed ictal scalp vEEG recordings and classified the seizures types into ES, TS, PS, SG (see definitions in next paragraph), or other. For patients with ES/TS, we reviewed the polyphasic δ/θ waves and electrodecremental activity on EEG and seizure duration on EMG.

2.5. Definitions of ES/TS and PS/SG on scalp vEEG records

2.5.1. Definition of ES/TS

In this study, we defined ES and TS as seizures with 1) short muscular contractions of < 3 s (ES) and > 3 s (TS) on EMG in the neck or shoulders with rhombus or tadpole shapes, and 2) diffuse polyphasic δ/θ waves at the beginning of the muscular contractions on vEEG (Fig. 1).

2.5.2. Definition of PS/SG

We defined PS and SG as seizures with 1) clinical manifestations of PS/SG on vEEG, and 2) focal rhythmic activity with evolution (PS and SG) and secondary generalization (only SG).

2.6. Statistical analyses

We used Mann-Whitney *U* tests for comparisons of clinical information and outcomes after 1 and 2 years of implantation between the ES/TS and PS/SG groups. We analyzed the correlations between seizure outcomes and the predictive factors. The clinical factors studied were the number of AEDs used before implantation, development, age of onset, time between onset and implantation, seizure frequency before implantation, and maximum current of VNS. We also obtained the mean duration of muscular contraction and the occurrence ratio of electrodecremental activity from the EMG data. We initially performed univariate ordinal logistic regression analysis. For predictive factors with *p*-values < 0.2, we then performed multiple ordinal logistic