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Early-onset response is a predictor of better long-term outcome of vagus nerve stimulation therapy

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Abstract

Background & Objective: It is well established that the effectiveness of vagus nerve stimulation (VNS) therapy increases over 2-3 years. When increasing the dose of VNS, some patients were noted to respond even at low-dose stimulation in the first few months. The purpose of this study was to evaluate the relationship between an initial response to VNS and long-term response in a retrospective study of patients with intractable epilepsy. *Method:* We retrospectively analysed 56 patients who had VNS implantation in our centre. All patients had undergone complete presurgical evaluation. After implantation, the patients were examined at regular intervals of one month for 6-9 months and then followed up regularly for more than 2 years. Their seizure frequency and intensity were documented in their seizure logs. *Results:* Six patients achieved Engel class I (11%) seizure outcome, 16 achieved Engel class II (28%), and 19 achieved Engel class III (34%). Of the 22 patients with Engel I and II, the 19 in Engel class I (100%) and II (81%) showed an initial response within 6 months, an early-onset response of VNS implantation.
Conclusions: Early-onset response could be an independent predictor for achievement of Engel class I and II in long-term follow-up.

Keyword: Vagus nerve stimulation, long term outcome, early onset response, predictor, epilepsy

INTRODUCTION

Vagus nerve stimulation (VNS) is an adjunctive therapy approved for use in patients with treatment-resistant epilepsy. Patients with treatment-resistant epilepsy who are not candidates for conventional surgery, or who refuse surgery, or failed to respond to other surgical or medical treatment could potentially benefit from VNS.[1-3] VNS may modulate the cortical excitability of regions associated with epileptogenesis and gamma-aminobutyric acid (GABA) receptor plasticity may contribute to the beneficial effect.[4,5] However, the mechanism by which VNS mediates an anti-seizure effect till to-date is unknown.

It is well established that the effectiveness of VNS increases over time, with progressive increase in the beneficial effect of VNS on seizures.[6] According to Morris *et al*., a more than 50% seizure reduction occurred in 36.8% of patients at 1 year, 43.2% at 2 years, and 42.7% at 3 years[7]; with some studies responding responder rates of 23-31% of patients after 3 months of acute VNS treatment.[8-10] Throughout our clinical experience with VNS treatment, we also noted that some patients had a positive response within several months. If we can recognize the factors that help to predict long-term outcome, we can encourage the patients to take the wait-and-see approach and continue VNS therapy even though the initial response is not dramatic, while others may be better off undergoing other treatment options including open cranial surgery and a ketogenic diet.

The purpose of this study is to evaluate the relationship between initial response to VNS and long-term response in a retrospective study of patients with intractable epilepsy.

METHODS

Between November 2011 and April 2014, 68 patients with treatment-resistant epilepsy underwent implantation of a VNS at the Seirei Hamamatsu General Hospital, Comprehensive Epilepsy Center. We created a database for clinical data storage. All patients had undergone complete presurgical evaluation, including a detailed clinical history, magnetic resonance imaging (MRI),

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and long-term video-electroencephalography (VEEG) with ictal and interictal recordings. We classified all patients by epilepsy type based on the International League Against Epilepsy (ILAE) 1989 classification. After implantation, all patients were examined at regular intervals of one month for 6-9 months, and then followed up at every two to three month for 2 years and more. All patients or caregivers had recorded their seizure frequency and intensity in their seizure logs.

Surgical procedure and outcome assessment

Surgical subcutaneous or subpectoral implantation of the VNS device (VNS Therapy® System, Cyberonics, Inc., Houston, TX, USA) was performed.[11] The stimulators were turned on 2 weeks after surgery, using the parameters current: 0.25 mA, frequency: 30 Hz, pulse width: 500 ms, 30-s signal on time, 5-min signal off time. After the first visit, follow-up occurred 1 month postoperatively until the full dose of the VNS generator was achieved. At each visit the current was gradually increased in steps of 0.25 mA. If patients showed no improvement of their seizures for 1 year after implantation, the current was gradually increased until the maximal possible output of 3mA or the signal off time from 5 min to 30 s. Long-term follow-up and adjustments of VNS parameters were conducted by pediatric neurologists (T. Okanishi, S. Kanai and H. Enoki), neurologist (K. Sato) and neurosurgeon (A. Fujimoto) in our centre.

Retrospective chart review was performed to collect follow-up and outcome data. All patients included in this study had at least 2 years of VNS therapy. Patients who did not have follow-up of at least 2 years, and patients who underwent open cranial surgery after VNS therapy were deemed to have inadequate follow-up and were excluded from outcome analyses.

There were 56 patients (36 men, 20 women; age range, 3-56 years; mean age, 24 years) included in this study. Epilepsy types were as follows: 28 patients with symptomatic generalized epilepsy (SGE), 16 with symptomatic localization related epilepsy (SLRE), 9 with SGE/SLRE, 1 with idiopathic generalized epilepsy (IGE)[12,13], and 2 with progressive myoclonic epilepsy (PME).[14] (Table 1)

Initial response to VNS was defined as an average of more than 10% reduction in seizure frequency from baseline. We also defined the initial response, which was obtained within six months as an early-onset response. We evaluated the long-term outcome of the VNS therapy based on Engel classification I-IV (Engel I: free of disabling seizures; Engel II: rare disabling seizures; Engel III: worthwhile improvement; Engel IV: no worthwhile improvement).[15] We also evaluated age at VNS implantation, sex and epilepsy type according to 1989 ILAE classification.

Statistical analysis

In the statistical analyses of clinical data, durations of initial response, and their correlation with the long-term outcome subgroup based on Engel classification, we used Welch t-test, Chi-square for independence test and Kruskal-Wallis test, appropriately. For the repeated analyses, we used Bonferroni correction. Multivariate ordinal logistic regression analysis was performed to determine the influence of the different variables on the response. We examined the relationships between the long-term outcome and age at VNS implantation, epilepsy type, sex or initial response. Statistical significance was set at $p < 0.05$. All analyses were done using JMP.

RESULTS

The clinical date was shown in Table 1. The relationship between the initial response and the long-term outcome was shown in the box-and-whisker diagram (Figure 1). Multivariate ordinal logistic regression analysis of the relationships between the long-term outcome and age at VNS implantation, epilepsy type, sex and initial response was shown in the Table 2.

Long-term outcome

Six patients (11%) obtained seizure freedom (Engel I), 16 (28%) had rare disabling seizures (Engel II), 19 (34%) attained worthwhile improvement (Engel III), and 15 (27%) were non-responders (Engel IV).

Initial response

Patients with Engel class I showed initial response at a mean of 3.5 months (range, 1-6 months). Patients with Engel class II showed initial response at a mean of 3.3 months (range, 1-8 months). Patients with Engel class III showed initial response at a mean of 11.2 months (range, 1-50 months). Patients with Engel class IV showed initial response at a mean of 42.6 months (range, 26-54 months) (Figure 1).

Table 1: Clinical information

Engel classification	I	II	III	IV
Number of patients	6(11%)	16(28%)	19(34%)	15(27%)
Sex (Female: Male)	2:4	6:10	7:12	5:10
Age at VNS implantation (mean, range)	30.5, 17-40	24.9, 4-27	24.7, 6-56	17.9, 3-47
Epilepsy type (Number of patients)				
SGE	1	6	11	10
SLRE	4	6	4	2
IGE	1	0	0	0
SLRE/SGE	0	2	4	3
PME	0	2	0	0
Initial Response (mean, range)	3.3, 1-6	3.2, 1-8	11.2, 1-50	42.5, 26-54

VNS: vagus nerve stimulation; SGE: symptomatic generalized epilepsy; SLRE: symptomatic localization related epilepsy; IGE: idiopathic generalized epilepsy; PME: progressive myoclonic epilepsy;

Within 6 months from stimulation initiation, 22 patients showed early-onset response. Among them, 6 patients were Engel class I (100%), 13 were Engel class II (81%), and 10 were Engel class III (53%). Conversely, no patients with Engel class IV exhibited early-onset response.

Epilepsy type

Patients with each Engel classification were subdivided based on epilepsy type. Engel I: 1 SGE, 4 SLRE, and 1 IGE; Engel II: 6 SGE, 2 SGE/SLRE, 2 PME, and 6 SLRE; Engel III: 11 SGE, 4 SGE/SLRE, and 4 SLRE; Engel IV: 10 SGE, 3 SGE/SLRE, and 2 SLRE.

Statistical analysis

In the statistical analyses for the clinical data, sex and age at VNS implantation were not significantly different among the long-term outcome subgroups. Regarding epilepsy types, less patients with SGE were in Engel I, as compared with those in Engel III (p=0.04) and IV (p=0.02). Other epilepsy types were not different among the long-term outcome groups.

The duration it take to achieve initial response in the subgroup of Engels IV was longer than those in the subgroups of Engel I, II and III (Figure 1; p<0.01 in all). We described the statistical analyses for the influence of the variables on the long-term outcome in Table 2. Early-onset

Table 2: Statistic analyses of predictors for long-term outcomes

	Estimate	Standard error	p-value
Age at VNS implantation (year old)	0.034	0.027	0.141
Sex	0.315	0.709	0.657
Initial Response (month)	–0.233	0.061	<0.001*
Epilepsy classification			
SGE	2.923	1.114	0.009*
SLRE	0.951	1.016	0.349
IGE	16.495	3490	0.996
PME	1.049	1.826	0.566

VNS: vagus nerve stimulation; SGE: symptomatic generalized epilepsy; SLRE: symptomatic localization related epilepsy; IGE: idiopathic generalized epilepsy; PME: progressive myoclonic epilepsy; *: significant correlations to the longterm outcome; Statistics: multivariate ordinal logistic regression analysis

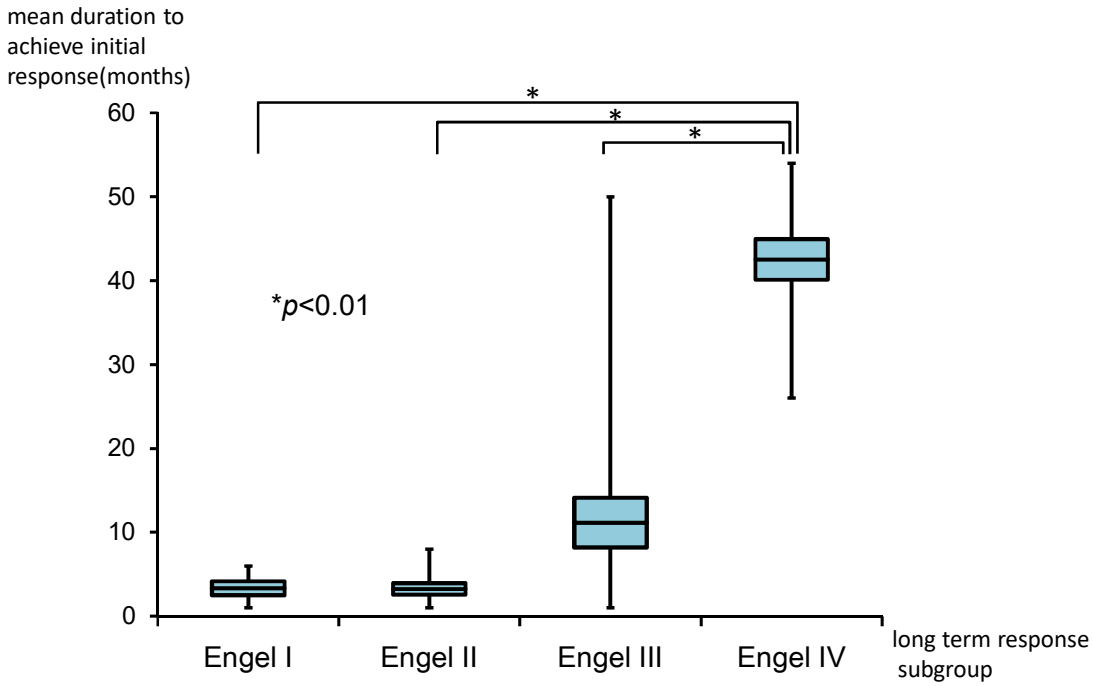

Figure 1: The relationship between long-term outcome subgroup and mean duration to achieve initial response are shown in the box-and-whisker diagram. The duration to achieve initial response in the subgroup of Engels IV was longer than those in the subgroups of Engel I, II and III (p<0.01 in all).

response was significantly correlated with better long-term outcome (p <0.001). The patients with SGE tended to show significantly worse long-term outcome (p=0.009). Other factors of age of VNS implantation, sex and epilepsy types other than SGE did not show significant correlations with long-term outcome.

DISCUSSION

It is well known that the effectiveness of VNS increases over time, with progressive improvement in the beneficial effect of VNS on seizures long term.[6] However, from the clinician's point of view, a better understanding of the factors predicting long-term outcome would be helpful in treating patients with intractable epilepsy because there are other treatment options including dietary therapy and open cranial surgery. Arcos *et al.* showed predictive factors such as temporal discharge and MRI lesions having better outcomes.[16] Some other positive predictive factors for VNS response include younger age at VNS implantation[17], focal EEG discharges[18], and symmetrical EEG findings.[19] We noted in this study, that even after a few months, some patients showed subtle positive response, of more than 10% reduction in seizure frequency. We referred to this as early-onset response, which was correlated to better long-term outcome. However, we must take into account that about 18% of patients with early-onset response, who did not achieve better long-term outcomes. This could be partly explained by a possible placebo effect. Nevertheless, according to a study by Uthman[20], some patients obtained VNS efficacy more than 10 years after implantation.[21] Thus, we must take into consideration the possible placebo effect, and improved outcomes in the long-term.

It has been said that VNS effect is produced by retrograde cerebral stimulation via the vagus nerve afferents, inducing increased synaptic activity in the locus coeruleus, raphe nuclei, and thalamus and its projections as well as other components of the central autonomic system. This results in a decrease in limbic system activity and an increase of some neurotransmitters such as norepinephrine and serotonin.[4,5,22,23] However, the mechanism of VNS treatment as well as the mechanism of early-onset response remains unknown.

The effectiveness of VNS has been shown not only for epilepsy, but also for depression, migraine[24,25], tinnitus[26], and other disorders. Some studies have shown that 20-30% of patients with major depressive disorder experienced VNS efficacy within 3 months.[8-10,24] Therefore, early-

onset response in patients with intractable epilepsy is not unique.

In conclusion, the early-onset response could be an independent predictor for achieving a Engel class I and II long-term seizure outcome.

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