Childs Nerv Syst (2016) 32:641–646
DOI 10.1007/s00381-015-3004-z

ORIGINAL PAPER

Long term effect of vagus nerve stimulation in pediatric intractable epilepsy: an extended follow-up

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Received: 27 November 2015 / Accepted: 23 December 2015 / Published online: 15 January 2016
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Abstract
Purpose Over the past two decades, vagus nerve stimulation (VNS) has become an accepted and viable treatment modality for intractable epilepsy both in children and adults. Earlier studies have demonstrated short-term seizure outcomes, usually for up to 5 years; so far, none have reported an extended outcome in children. We aimed to assess long term seizure outcome in children with intractable epilepsy for more than 5 years.
Methods We identified patients who had VNS implantation for treatment of intractable epilepsy from March 2000 to March 2015 at our Epilepsy Center and collected data including demographic, age at epilepsy onset and VNS implantation, duration of epilepsy, seizure type, number of antiepilepsy drugs (AEDs), and monthly seizure frequency before VNS implantation and at the last clinic visit. Phone surveys were conducted with patients without recent clinic follow-up.
Results Fifty-six patients (aged 4–17 at the time of implant) are the subjects of the study. Seizure reduction of >50 % was achieved in 9.8 % (6th month), 24 % (2nd year), 46.4 % (3rd year), and 54 %(5th year), and overall 35 (62.5 %) of the 56 subjects had a greater than 50 % reduction in seizure frequency at the last follow-up. Eleven patients became seizure free. The results, once obtained, were maintained steadily or even improved over time without any loss of efficacy during the follow-up. The only parameter, significantly related with clinical response, was age at seizure onset. The most frequent adverse events were hoarseness, cough, sore throat, and anorexia, experienced by 13 patients. Two patients had local wound infections and lead to the removal of the stimulator. An improvement in alertness, attention, and psychomotor activity, independent of the efficacy of vagal nerve stimulation, was observed in 8 patients.
Conclusion To our knowledge, this is the first pediatric study evaluating seizure outcome over more than 5 years of follow-up, and demonstrates a favorable seizure outcome of >50 % seizure frequency in 62.5 % of patients and seizure freedom in 11 patients. It is well tolerated over an extended period of time.

Keywords Intractable epilepsy · Pediatrics · Vagal nerve stimulation

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Introduction

Despite optimal medical management with appropriate antiepileptic drugs, 10–30 % of children with epilepsy continue to suffer from seizures [1–3]. Uncontrolled seizures heavily impact on the patients' functional neurodevelopment and subsequent quality of life. Considering the cumulative effect and reduction in seizure frequency and severity, vagus nerve stimulation (VNS) has become a valuable, modern option in the therapeutic armamentarium for patients with intractable epilepsy [4].

Efficacy of VNS therapy in the treatment of epilepsy is now well established, showing improvement in seizure

control and quality of life. Subsequent studies have reported seizure outcomes for up to 5 years [5–12] and rarely to 10–11 years [13]. So far, there is no data assessing the long term seizure outcome in children with intractable epilepsy for more than 5 years. The aim of our study was to determine the seizure outcome of these patients at the end of the extended follow-up period and the factors correlated with this outcome. This study was, to some extent, a continuation of the assessment of long term outcomes of VNS therapy for intractable epilepsy at our center [14].

Material and method

Patients who had VNS implantation for intractable epilepsy from March 2000 to March 2015 were retrospectively identified from our Epilepsy Center database. Patient data was entered into a database and was available for subsequent analysis in our Epilepsy Center. Standardized seizure-frequency forms, which were used at each VNS-related visit, are used for data collection. Monthly seizure-frequency data were obtained from patients, parents, and/or care-givers. In patients with more than one type of seizures, data were collected for overall monthly seizure-frequencies. A retrospective data review was undertaken to identify patients with a follow-up period of 5 years or more. The enrolled study patients had been implanted with the VNS therapy device between 21 March 2000 and 20 March 2010. A total of 59 patients with intractable epilepsy were implanted with a VNS system at Gazi University Faculty of Medicine Epilepsy Center during this period. Three patients died during follow-up; 56 patients comprised the study population.

The data collected from the medical records included demographic variables, etiology of the epilepsy, and results of all diagnostic workup. Specifically, we collected age at onset of epilepsy and at the time of VNS implantation, duration of epilepsy, and seizure type (generalized or partial). In addition, we evaluated monthly seizure frequency data in each visit, epilepsy treatment regimen, magnet use, and effectiveness and side effects of VNS. We also recorded the results of the magnetic resonance imaging (MRI). Phone surveys were conducted with patients without recent clinic follow-up. In a structured survey, parents were asked about seizure frequency, antiepileptic drugs and side effects in the last few years. We specifically inquired about their current monthly seizure frequency, changes in seizure semiology, and current treatment regimen for epilepsy.

To evaluate the efficacy of VNS, we assessed the changes in seizure severity over time based on the available patient records and phone surveys. Assessments of seizure duration, ictal severity, and postictal severity were categorized as "decreased," "unchanged," "increased," or "unknown." The seizure frequency reduction was straffied as seizure frequency reduction more than 75 %, between 50 and 75 %, less than 25 %, no change, or worsening. We considered the group who have more than 50 % seizure frequency reduction as responder group, while others as non-responder group.

All patients had a stable anti-epileptic drug regimen during the first year of VNS. After 1 year, drug adjustments were permitted. During the period of drug adjustments VNS parameters did not change for several months in order to evaluate the effect of drug changes only.

All analyses were performed using SPSS software for Windows (version 15.0, SPSS Inc., Chicago, IL, USA). Spearman's correlations were used to determine the association between age at seizure onset, age at VNS implantation, duration of epilepsy prior to VNS implantation, duration of intractable epilepsy, follow-up, and percentage seizure reduction in seizure frequency in these patients. For each year of follow-up, the frequency of seizures was calculated as a percentage of baseline and these percentages were entered into the repeated measurements analysis. Mann-Whitney *U* test was used to compare variables between seizure-free patients and other patients. We used chi-square to compare proportions.

Results

Demographics

A total of 59 patients with epilepsy were identified as having VNS implantation between 2000 and 2010. Three patients died during follow-up. The remaining 56 patients (23 female, 33 male) are the subjects of the study.

The mean follow-up was 87.22 months (SD ± 3.72 months). Mean age at implantation was 10.96 (SD ± 3.56 years range 4–17). Median age at onset of epilepsy was 2 years (ranging from 2 months to 10 years of age, SD = 2.8) and median duration of epilepsy (at the time of implantation) was 8.0 years (ranging from 1.9 to 15 years, SD = 3.4) (Table 1).

The etiology of the epilepsy was identified in 18 patients: prematurity and perinatal anoxic/ischemic lesions in 8(14.2 %), neonatal hypoglycemia in 2 (3.57 %), kernicterus in 1 (1.78 %), intracranial empyema 1 (1.78 %), encephalitis/meningitis in 3 (5.35 %), tuberosclerosis in 1 (1.78 %), intrauterine infection in 1 (1.78 %), Rasmussen encephalitis in 1 (1.78 %), and neuronal ceroid lipofuscinosis in 1 (1.78 %). The etiology was unknown in the majority of the patients (67.8 %) (Table 1). One patient with hippocampal sclerosis had VNS implantation 4 years after anterior temporal lobectomy and one patient with Rasmussen encephalitis had hemispherotomy 2 years before VNS implantation.

All patients had a routine and prolonged video-EEG evaluation. Electroencephalography with routine and prolonged

Table 1 Demographic data of the patients

Patient characteristics	
Number of patients	n = 56 (33 males, 23 females)
Age at onset of epilepsy	2 months to 10 years, 2.2 ± 2.8 years (mean ± SD)
Age at implantation	4–17 years, 10.96 ± 3.56 (mean ± SD)
Length of follow-up	60–186 months, 87.22 months, 3.72 (mean ± SD)
Etiology	
Unknown	40
Prematurity, anoxic ischemic lesions	8
Menengitis, encephalitis	3
Neonatal hypoglycemia	2
Kernicterus	1
Intracranial ampiem	1
Rasmussen encephalitis	1
Neuronal cerid liofuscinozis	1
Tuberosclerosis	1
Intrauterine infection	1
Landau Kleffner	1
Co-morbidities	
Mental retardation	41
Autism	5
Febrile convulsion	3
Hearing loss	1
Cerebral palsy	3

video-EEG evaluations showed evidence for a focal epilepsy in 36 (61 %), multifocal epilepsy in 13 (22 %), and generalized epilepsy in 10 (17 %) patients. Seizure types included generalized tonic-clonic and other generalized seizures (myoclonic, absence, and atonic seizures) in 64.4 % and complex partial and focal motor seizures in 15.3 %, and mixed types were noted in 12 (20.3 %) patients (Table 1).

MRI findings consisted of encephalomalasia and gliosis in 9 (16.07 %), followed by brain atrophy in 8 (14.2 %), malformations of cortical development (pachygyria, schizencephaly) in 3 (5.35 %), cortical tubers and findings consistent with tuberous sclerosis complex in 1 (1.78 %), hippocampal sclerosis in 1 (1.78 %), arachnoid cyst in 1 (1.78 %), and Dandy Walker variant in 1 (1.78 %). No structural abnormalities were evident on MRI in 32 patients.

Efficacy

Seizure reduction of >50 % was achieved in 9.8 % (6th month), 24 % (2nd year), 46.4 % (3rd year), and 54 % (5th year), and overall, 35 (62.5 %) of the 56 subjects had a greater than 50 % reduction in seizure frequency at the last follow-up. In 17 of them, the reduction was greater than 75 %. Eleven patients became seizure free. The results, once obtained, were maintained steadily or even improved over time without any loss of efficacy during the follow-up. Eighteen patients (32.1 %) reported a reduction less than 50 %, seven (12.5 %) had less than 25 % reduction, and two patients had no change in the number of seizures. (Fig. 1) The non-responder subjects had a very high seizure frequency (more than 10/day). The duration of epilepsy before VNS implantation did not have a significant difference between the responder and non-responder group. The examined parameters including, age at VNS implantation, duration of epilepsy, and seizure type were not found to be significantly related to clinical response. The only parameter which was significantly related with clinical response was age at seizure onset. Poor clinical response was seen in patients with early seizure onset (p = 0.021) (Spearman correlation). In addition, ictal and postictal severities decreased in about 10 (17.8 %) of patients over time. In the responder group, when we compared the reduction in the number of different seizure types (generalized, focal, myoclonic and atonic), there was a significant difference in reduction means between atonic and generalized tonic clonic seizures (p = 0.023).

Seizure freedom was achieved in 11 patients. Four of these patients achieved seizure freedom in the first 2–3 years. In these patients, we found a positive relation association between the age of the patients at the time of implantation of the stimulator and clinical response (p = 001) (Mann-Whitney U test). Seven of these patients were below 12 years of age at the time of implantation, and

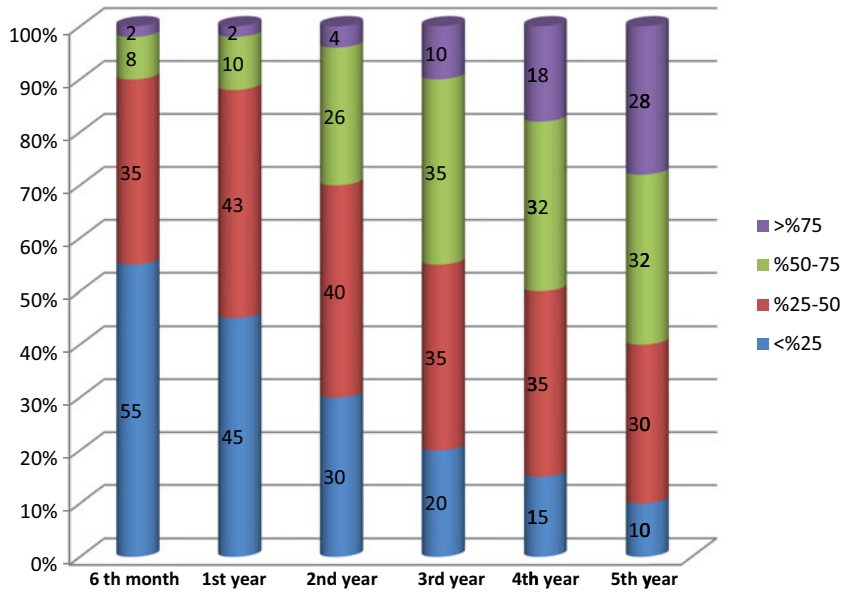


Fig. 1 Proportional change of seizure frequency during the follow-up period. The number of responder (patients with <50 % seizure frequency reduction after VNS implantaion) increased from 9.8 % at the first 6 months to 62.5 % at the fifth year follow-up

all patients who became seizure-free showed a complete normalization of the EEG abnormalities. There was no significant difference in relation to the type of seizures. When these patients were evaluated in terms of predictive factors such as intellectual disability and a "causative" lesion on magnetic resonance imaging (MRI), only two of them had moderate intellectual disability and two have a lesion on MRI, one hippocampal sclerosis and one gliosis.

Drug regimen

Forty-six patients stayed on a stable anti-epileptic drug regimen. Three patients stopped using levetiracetam when his seizure frequency was reduced by 50 %, and remained stable in the follow-up. Another patient with 75 % seizure frequency reduction after 1 year experienced a mild but gradual diminishing effect of VNS. Five patients started clobasam after 2–3 years of VNS. During the 6-month follow-up period in these patients, a minimal decrease in seizure frequency was noticed. One patient, with an initial effect of 40 % seizure reduction with VNS, started topiramate after 4 years of VNS, when seizures became more frequent. However, no obvious change in seizure frequency was noted.

Device removal and battery replacements

Two patients had their devices removed because of device-related infections (mechanical failure) and one patient had battery replacement because of functional lead impedance problem (Table 2).

Complications

The most frequent adverse events were hoarseness, cough, sore throat, and anorexia, experienced by 13 patients (23.1.0 %).) During the study period, three patients died. One patient who had no seizure reduction died after 2 years of follow-up possibly as a result of SUDEP. The relationship of SUDEP and VNS in this patient is not known. Two patients died because of sepsis and pneumonia. One patient had a subcutaneous hematoma which did not require device removal.

In eight patients, an improvement in alertness, attention, and psychomotor activity compared with the pre-implantation status was observed, independent from the efficacy of VNS in reducing seizure frequency (two had a reduction ≥50 %; three had a reduction <50 %; two remained unchanged).

Discussion

As a VNS efficacy study, this study is unprecedented in terms of its duration and length of clinical follow-up (average of 88 months). Most published VNS efficacy studies have reported prospectively and/or retrospectively, on the order of 5 years or less.

To our knowledge, this is the first pediatric study assessing the long term impact of VNS therapy on seizure outcomes more than 5 years for epilepsy. Our findings reveal that adjunct VNS therapy leads to 50 % or more seizure reduction in 62.8 % and seizure freedom in 20 % of patients. The results are promising in such a group of severely affected epileptic

Table 2 Adverse events with VNS

Mechanical/functional	Total	Self-limiting	Revision required
Local infection at the side of the implantation (Mechanical)	2	–	2
Sore throat	1	1	–
Hoarseness	3	3	–
Lead impedance problem (functional)	1	–	1
Subcutaneous hematoma at the site of implantation (mechanical)	1	1	–
VNS ON			
Speech problems	1	1	–
SUDEP	1	–	–
Hoarseness	1	1	–
Cough	2	2	–
Anorexia	1	1	–

patients who often have more than one type of seizure occurring more than once per day and with a long history of disease.

Despite similar overall efficacy results, the acute 6-month responder rates of 9.8 % in our study are lower than the literature data [6, 10, 15–18]. More favorable responses of 23–31 % after an acute 3 months of VNS treatment have been reported from other retrospective studies [19, 20]. We excluded the first 3 months from the analysis because of our longer ramp-up period. The lower response rate in the first 6 months may be due to this longer ramp-up period. When the study follow-up period is extended, the response rates are increased 24 % at 24 months, and 46.4 % at 36 months, and overall seizure reduction of 62.5 %. long term efficacy results from previous studies support our findings with response rates of 59 % (27/46, duration of follow-up ranged from 6 to 60 months), 64 % (83/128; median follow-up of 5.2 years), and 68 % (26/38; median follow-up of 12 months) [10, 17, 21]. These data indicate that VNS efficacy increases and maintains over time. There is a possible relation between the duration of VNS period and the effect of seizure reduction, as previously reported [13, 17, 22].

Many of the previous reports on VNS efficacy in children did not mention the results based on each different seizure type; hence, it was difficult to compare our results with these. Results of previous studies show a heterogeneous seizure type control rates, although it seems that generalized tonic-clonic and myoclonic seizures responded better to VNS [15, 23, 24]. Patients in our study had multiple distinct seizure types, and in contrast with these previous reports, generalized tonic-clonic and atonic seizures had a favorable outcome with VNS therapy. These results highlight the importance of reporting and analyzing seizure frequency reduction by seizure type and not by individual patient.

Interestingly, the number of seizure free patients at follow-up was higher compared to that of earlier studies [5, 16, 11, 25, 26]. Possible explanations for this may be the introduction of several new antiepileptic drugs during the past decade and refinement of the VNS techniques. We propose that this also is a result of the longer follow-up in our study. We considered the possibility that other factors such as intellectual disability and causative brain lesions may have influenced the prognosis and the occurrence of intellectual disability and MRI lesions were less prevalent in this group and this may have lead to the maintenance of a seizure-free state.

It is well documented that VNS may have a positive effect on psychomotor activity, often independent of seizure reduction. Based on the clinician's assessment of the patients' overall condition and parent reports, eight patients in our group were considered to improve in alertness, attention, and psychomotor activity independent from the efficacy of VNS in reducing seizure frequency. This may be a direct effect of VNS on behavior and attention [27, 28]. Therefore, even in the presence of minimal or no seizure reduction in seizure frequency, a patient can have significant improvement in alertness, attention, and concentration which may be due to less severe seizures or fewer episodes of status epilepticus with hospital visits or admissions and the development of seizure-free days.

VNS has been proven to be safe, well tolerated, and usually not associated with the common central nervous system adverse effects [22, 29–31]. Most patients in our group become accustomed to mild and transient stimulation-related side effects like by vocal hoarseness, sore throat, paresthesiae, and coughing, occurring only during stimulation, with a tolerance developing over time. Complications associated with implantation have included infection at the incision site, lead impedance problem, and transient paralysis of the left vocal cord [29, 30]. Our results are consistent with the literature [22, 29, 30].

Our study has clear limitations. First of all, our study has a retrospective and uncontrolled design. Indeed, VNS literature suffers from the lack of randomized controlled trials examining longer-term outcomes. We agree with previous investigators who prompt us to interpret these results with caution

because of the uncontrolled design. A second limitation is that patient assessment in this series was not blinded and seizure-frequency data was based on reporting by patients and/or families and clinician's assessment.

Despite the above limitations, we have shown the effectiveness and well tolerability of VNS in a large cohort of pediatric patients with an extended follow-up period. The size of the cohort and the length of follow-up are advantages of our study. The results of our study are consistent with the results of current literature which seizure reduction demonstrated time dependence. Furthermore, our findings demonstrate that the benefits of VNS treatment may extend beyond the sole reduction in seizure frequency. Higher response rates were observed for the subset of patients who have no co-morbid disorders or brain imaging abnormalities.

Compliance with ethical standards

Conflict of interest This study was approved by the local ethics committee.

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