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Vagus nerve stimulation for medically refractory absence epilepsy

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ABSTRACT

Purpose: A proportion of patients with childhood and juvenile absence epilepsies (CAE, JAE) are likely to be classified as medically refractory. In view of evidence gap for the treatment of such patients, this series is reported to generate estimate for efficacy of vagus nerve stimulation (VNS) in this patient population.
Methods: Patients were identified by a chart review of all VNS recipients between January 1, 2006 and December 31, 2011. The diagnosis of CAE and JAE was based on conventional criteria. Details of demography, epilepsy phenomenology, management and outcomes were extracted. The outcome measures included reduction in daily seizure frequency measured as a percentage of pre-VNS seizure frequency and classified on International League Against Epilepsy (ILAE) outcome scale.
Results: Nine patients (7 CAE, 2 JAE) with a mean age of seizure onset of 5.4 years (±3.9) were identified. Mean duration of epilepsy prior to VNS implant was found to be 3.9 years (±1.4). These patients had failed a median of 5 anti-epileptic drugs before being referred for consideration of surgical treatment. After a mean follow-up of 33.9 months (±25.5, minimum 4 months), 1 patient attained complete seizure freedom (ILAE class 1), 6 had ILAE class 4 and 2 had ILAE class 5 outcomes, respectively. Mean reduction in daily seizure frequency was found to be 53.5 ± 60.3% (1-sided p-value for paired t-test = 0.04), with a 50% responder rate of 55.6%.
Conclusion: VNS may be considered as a therapeutic option in patients with medically refractory absence epilepsy.

1. Introduction

Absence seizures, characterized by frequent brief staring episodes, are commonly encountered in a number of pediatric idiopathic generalized epilepsy syndromes including childhood and juvenile absence epilepsies (CAE, JAE), and juvenile myoclonic epilepsy. Usually, CAE and JAE are considered benign, drug responsive, age-limited entities. However, up to 20% of patients may not achieve seizure remission with adequate drug therapy.[1] In the landmark CAE study, the freedom-from-failure rates were 53% and 58%, respectively for ethosuximide and valproic acid, after 16 weeks of therapy.[2] Thus, a proportion of patients with these syndromes may qualify as having drug resistant epilepsy by International League Against Epilepsy (ILAE) definition.[3] Further, approximately 10% of patients with CAE and 24% with JAE do not experience age related remission.[4] There is markedly limited information about management of such patients with medically refractory absence epilepsies. In a recent series of 12 patients, 6 (50%) had >90% seizure reduction at 12 months of treatment with amantadine.[5] However, in this study, 3 patients discontinued amantadine within 6 months due to lack of efficacy. Three additional patients reported significant adverse effects including behavioral changes, headache, dizziness and weight loss.[5] There have been 2 earlier isolated uncontrolled reports of use of amantadine for absence seizures unresponsive to usual AED.[6,7] Besides these studies, there is paucity of evidence for efficacy of other treatment options for children with medically refractory absence epilepsies.

These epilepsies have primarily generalized ictal onset and these patients are not usually thought to be candidates for resective epilepsy surgery. However, vagus nerve stimulation (VNS) has been tried in adults with medically refractory generalized epilepsies including patients with absence seizures. In a series of 12 patients, 58% decrease in frequency of absence seizures was noted after a mean follow-up of 23 months.[8] In some other reports of use of VNS for treatment of adults with medically refractory generalized epilepsy, the outcome for absence seizures

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Table 1
Clinical profiles and outcomes of patients with refractory absence epilepsy treated with vagus nerve stimulation.

Patient #	Age (years)	Sex	Age at SZ onset (years)	Age at VNS (years)	Duration (years)	Frequency (per day)	AED#	AED at referral (past)	Follow-up (months)	ILAE outcome	% Reduction	EEG outcome
1	28	M	–	23.39	–	25	3	LTG, VPA	LOST	5	40	No change
2	14	M	6	9.47	3.47	200	3	FLB, ZNS	62	4	90	Improved
3	13	M	4.5	8.42	3.92	24	4	LTG	61	4	55	No change
4	13	M	4.5	8.42	3.92	10	4	LTG	56	4	55	No change
5	9	M	1.8	4.28	2.48	15	5	CLN, LTG, VPA	47	1	100	Improved
6	13	F	8	11.25	3.25	23	6	PHT (GBP, FLB, LEV, TPM, VPA)	26	5	−74	Worse
7	9	M	0.5	7.26	6.76	50	21	LOR, RUF, VPA (18 OTHER AED)	4	4	80	Improved
8	12	M	5	9.53	4.53	100	8	AMANTADINE (CLN, ETX, LEV, LTG, OXC, TPM, ZNS)	7	4	50	No change
9	17	F	13	15.61	2.61	60	5	ETX, FLB, LEV, LOR	8	4	88	Improved

AED: anti-epileptic drug; ILAE: International League Against Epilepsy; SZ: seizure; VNS: vagus nerve stimulation; CLN: clonazepam; GBP: gabapentin; ETX: ethosuximide; FLB: felbamate; LEV: levetiracetam; LOR: lorazepam; LTG: lamotrigine; OXC: oxcarbazepine; PHT: phenytoin; RUF: rufinamide; TPM: topiramate; VPA: valproate; ZNS: zonisamide.

was not presented.[9,10] In view of this evidence gap, particularly in children, this case series is reported to estimate the efficacy of VNS in patients with medically refractory absence epilepsy.

2. Methods

Patients were identified by a retrospective chart review of all VNS device recipients between January 1, 2006 and December 31, 2011. The lower cut-off date was chosen because electronic medical records (EMR) system was installed at that time ensuring uniformity of information and ease of access. Additionally, since then all the VNS device insertions were performed by a single neurosurgeon (FTM). All patients diagnosed with absence epilepsy based on clinical features, EEG findings and a normal MRI of the brain, were eligible for inclusion if they received a VNS during the study period. Specifically, the diagnosis of CAE/JAE was based on ILAE revised classification of epilepsy syndromes, including frequent clinical absence seizures and characteristic EEG pattern.[11]

The extracted data comprised of demographic variables including age, sex, age at onset of seizures, duration of epilepsy prior to VNS implant, age at VNS implant; and, clinical details including daily seizure frequency, seizure types in addition to absence seizures, developmental delay or intellectual disability, epilepsy syndrome, and failed AED including those at referral. Both initial and follow-up seizure frequencies obtained from EMR charts were based on parental reporting. The outcome measures included reduction in daily seizure frequency measured as a percentage of pre-VNS seizure frequency and classified on ILAE outcome scale.[12] Lengths of follow-up and technical complications related to VNS device were also noted. EEG outcome was obtained from reports available in EMR for routine EEG. It was classified as improved, unchanged or worse based on frequency and duration of spike-wave bursts, and, presence, number and duration of electrographic or electro-clinical seizures. The data was recorded in an Excel (Microsoft Corp., Redmond, WA) spreadsheet. Appropriate summary statistics were calculated for all variables.

Neurocybernetic prosthesis (NCP) system (Cyberonics Inc., Houston, TX), implanted with standard surgical technique was used for left vagus nerve stimulation.[13,14] The device was switched on in immediate post-operative period with the following settings: current 0.25 mA, frequency 20–30 Hz, pulse width 250–500 μs, on time 30 s, off time 5 min. At follow-up visits every 1–3 months, the current was gradually increased by 0.25 mA until patient tolerance, seizure freedom or a maximum of 2.5 mA was achieved. The magnet output current was always programmed to be 0.25–0.5 mA higher than automatic stimulation, with a pulse width of 500 μs for a period of 60 s. Changes in concurrent anti-seizure medications or the decision to go for "rapid cycling", were at the discretion of treating neurologist.

3. Results

A total of 9 patients (7 males) with a mean age of 14.2 years (±5.7) were found, with mean age of seizure onset of 5.4 years (±3.9). The mean duration of epilepsy prior to VNS implant in these patients was 3.9 years (±1.4), with the mean age at VNS implantation being 10.8 years (±5.6). Clinically, 7 of the patients were classified as having CAE and 2 as JAE. The median seizure frequency based on parental reporting was found to be 25/day (inter-quartile range 61). Although 3 of the patients had generalized tonic–clonic seizures (GTCS) in addition to absence seizures, only 1 had a past history of status epilepticus. Two of the patients had borderline to mild developmental delay or intellectual disability. Prior to surgical referral, these patients had failed 3–21 AED (median = 5, Table 1). Three patients had functional neuroimaging as a part of their pre-surgical evaluation, which showed discordant data among different modalities.

These patients had follow-up for a mean duration of 33.9 months (±25.5, minimum 4 months). One patient attained complete seizure freedom (ILAE class 1), 6 had ILAE class 4 and 2 had class 5 outcomes, respectively. Mean reduction in daily seizure frequency was observed to be 53.5 ± 60.3% (1-sided p-value for paired t-test = 0.04), with 5 patients (55.6%) having a reduction of ≥50%. Only 1 patient had increased seizure frequency after a follow-up of 26 months (Table 1). EEG improved in 4 (44.4%) patients, with complete normalization in 1 (patient with complete seizure remission). It was classified as unchanged in 4 (44.4%) other patients, though on subjective review there was reduction in frequency of spike-wave bursts. One patient showed worsening of EEG with deterioration of background rhythm (patient with increased seizure frequency, Table 1). Two patients (22.2%) had lead fractures as a device related adverse event and the hardware needed to be replaced.

4. Discussion

This case series provides preliminary evidence for efficacy of VNS in children with medically refractory absence epilepsy, with 54% mean reduction in daily seizure frequency and a 50% responder rate of 56%, after a mean follow-up of about 3 years. The EEG outcome showed agreement with clinical response (Table 1). Our observations broadly agree with previously published experience with VNS in refractory idiopathic generalized epilepsy (IGE). In the E04 cohort, there was 60% reduction in mixed seizure burden in 7 patients with