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SHORT COMMUNICATION

# Vagus nerve stimulation in children less than 3 years with medically intractable epilepsy

Luis Fernandez[a], Satyanarayana Gedela[a,b], Mandeep Tamber[c], Yoshimi Sogawa[a,b,*]

[a] Division of Child Neurology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, United States
[b] University of Pittsburgh, School of Medicine, Department of Pediatrics and Neurology, Pittsburgh, PA, United States
[c] University of Pittsburgh, School of Medicine, Department of Neurosurgery, Pittsburgh, PA, United States

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**Abstract**
*Objective:* To describe the characteristics of children less than three years of age with medically intractable epilepsy, who underwent Vagus Nerve Stimulator (VNS) therapy at Children's Hospital of Pittsburgh between 2004 and 2011. Methods: Retrospective chart review. Results: Seventeen patients were identified; adequate follow-up was available for 15. Median follow up duration was 4.3 years (1.4—10.2 years). 12/15 (80%) had a known etiology for their epilepsy. All patients had more than 1 seizure per week prior to VNS and a history of status epilepticus was frequent (40%, 6/15). Five patients (33%) reported improved seizure frequency at one year after VNS. A normal MRI was associated with seizure improvement ($p = 0.007$). No patient had status epilepticus after VNS at one-year follow-up. At three years after VNS, four patients had experienced status epilepticus with only one patient experiencing multiple episodes. Complications were seen in 2/15 (13%) patients and in 2/21 (9.5%) procedures. Significance: A normal MRI was associated with seizure improvement at one year in children less than three years of age at the time of VNS implant. The degree of overall seizure reduction was modest, but the frequency of status epilepticus was decreased after VNS implant. VNS was tolerated well in this age group.


*Abbreviations:* VNS, vagus nerve stimulator; ILAE, international league against epilepsy; AED, antiepileptic drug.

* Corresponding author at: Children's Hospital of Pittsburgh of UPMC 4401 Penn Avenue, Faculty Pavilion-Floor 8 Pittsburgh, PA 15224, United States. Tel.: +1 412 692 5520; fax: +1 412 692 6787.
*E-mail addresses:* Yoshimi.Sogawa@chp.edu, YoshimiSogawa@gmail.com (Y. Sogawa).

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## Introduction

The utility of resective surgery is often limited in children with medically refractory epilepsy due to a known (symptomatic) etiology with a mixed seizure phenotype (Nordli, 2012; Wirrell et al., 2013). Therefore, VNS has been used as an adjunctive treatment for intractable epilepsy in both adults and children (Murphy et al., 2003; Morris et al., 2013). We describe the clinical characteristics and outcomes of children less than 3 years of age with medically intractable epilepsy who underwent VNS implantation as adjunctive therapy.

## Methods

For the period 2004—2011, children with medically intractable epilepsy who were less than 3 years of age when they underwent VNS placement at Children's Hospital of Pittsburgh were identified. The primary outcome was the change in seizure frequency at one year after VNS implantation. Seizure frequency was categorized as (1) daily multiple seizures, (2) less than daily but more than 1 seizure per week, (3) less than 1 seizure per week but more than 1 seizure per month, and (4) less than 1 seizure per month. Seizure type was categorized as generalized convulsive, drop, tonic, myoclonic, absence, atonic, focal or epileptic spasms, and was collected on each visit after VNS implantation, which was typically every 2—4 weeks for the initial 3 months and every 1—3 months thereafter. All seizure types were combined to determine seizure frequency. Seizures were judged as improved/unchanged/worsened based on the change in seizure frequency category. One year was chosen because VNS adjustment typically takes more than six months (Morris et al., 2013).

Etiology was dichotomized into known and unknown based on the revised ILAE Classification (Berg et al., 2010). A known etiology was further subdivided into (1) congenital or genetic brain malformation, (2) genetic without brain malformation, (3) perinatal/acquired brain insult and (4) known etiology, not otherwise specified. This last group was designated for children with clearly abnormal neurological examination or developmental history prior to the epilepsy onset, or children with genetic or MRI abnormalities of unclear clinical/etiological significance. Epilepsy syndrome at the time of surgery was classified by the investigators based on medical record and actual EEG review, according to the 1989 ILAE Classification (ILAE, 1989).

Status epilepticus was defined as either (1) a documented episode of status epilepticus (2) a seizure that persisted upon arrival to ED or (3) a seizure longer than 10 min in duration with active motor manifestations (Hesdorffer et al., 2011).

Among the various VNS setting parameters, Output current (mA), Duty cycle, and $Q_{Total}$ were analyzed. In addition, rapid cycling, which was defined as an off time <0.3 min, was treated as a categorical variable. $Q_{Total}$ was calculated as follows to represent the total amount of charge delivered per day (Aaronson et al., 2013).

$$Q_{Total} = \frac{\left(T_{period}\left(\frac{1}{1000}\right)\left(\frac{PW}{10^6}\right) f\,(t_{ON}+4)\right)}{t_{ON}+(t_{OFF}\times 60)}$$

$T_{period}$ = 86,000 s, such that $Q_{Total}$ represented the charge delivered per day. $f$ = output current (mA), $P_{W}$ = pulse width (μs), $f$ = pulse frequency (Hz), $t_{ON}$ = On time (S), and $t_{OFF}$ = OFF time (min). Four seconds were added to the ON time to account for ramping periods during the initiation and termination of simulation bursts (Aaronson et al., 2013).

Data analysis was performed with Stata software version 10 (StataCorp LP, College Station, TX). A two-sided $p$ value of <0.05 was considered statistically significant. Nonparametric tests were used because of small sample size, along with the Pearson chi-square or Fisher exact tests were used. This study was approved by the Institutional Review Board of Children's Hospital of Pittsburgh.

## Results

### Baseline characteristics ()

Tables 1 and 3 Seventeen patients were identified. Data from 15 patients was analyzed as two patients did not have sufficient information or follow up. The median age of seizure onset was 3.5 months and the median age at surgery was 26 months. The majority had a known epilepsy etiology (80%, 12/15) and generalized/mixed epilepsy (87%, 13/15). Two patients with focal epilepsy had bilateral or multifocal seizure onset.

### Seizure characteristics pre/post VNS

(Tables 2 and 3 )All patients had more than 1 seizure per week and more than two types of seizures at baseline. Seizures were captured in 93% (14/15) of patients during video-EEG monitoring prior to VNS surgery. Five patients (33%, 5/15) reported improved seizure frequency at one year after VNS implant but none became seizure free. The underlying epilepsy syndrome in these five patients was Dravet syndrome (3), generalized epilepsy NOS (1) and focal epilepsy (1). A normal MRI was associated with an improvement in seizure frequency (5/7 normal vs. 0/8 abnormal, $p$ = 0.007). Improvement in seizure frequency was not associated with etiology (4/12 known vs. 1/3 unknown, $p$ = 1.0). Generalized convulsive seizures were seen in 10 patients (67%) before VNS implantation and five patients after VNS implantation (33%). This improvement was not associated with overall improvement in seizure frequency ($p$ = 0.52), normal MRI ($p$ = 1.0) or known/unknown etiology ($p$ = 0.52). Four children, including three with Dravet syndrome, had multiple (up to eight) episodes of status epilepticus prior to VNS implantation. No patient had status epilepticus over 12 months after VNS. Four patients had status epilepticus at three years, but only one patient had multiple episodes of status epilepticus.

### VNS parameters

There was no statistically significant association between categorical seizure improvement at one year and output current ($p$ = 0.08), Duty cycle ($p$ = 0.1), $Q_{Total}$ ($p$ = 0.85) or rapid cycle ($p$ = 0.56).