Original Article

Early Implantation as a Main Predictor of Response to Vagus Nerve Stimulation in Childhood-Onset Refractory Epilepsy

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Abstract

Objective: We describe a multicenter experience with vagus nerve stimulator implantation in pediatric patients with drug-resistant epilepsy. Our goal was to assess vagus nerve stimulation efficacy and identify potential predictors of favorable outcome. **Methods:** This is a retrospective study. Inclusion criteria: ≤18 years at time of vagus nerve stimulator implantation, at least 1 year of follow-up. All patients were previously found to be unsuitable for an excisional procedure. Favorable clinical outcome and effective vagus nerve stimulation therapy were defined as seizure reduction >50%. Outcome data were reviewed at 1, 2, 3, and 5 years after vagus nerve stimulator implantation. Fisher exact test and multiple logistic regression analysis were employed. **Results:** Eighty-nine patients met inclusion criteria. Responder rate (seizure frequency reduction >50%) at 1-year follow-up was 25.8% (4.5% seizure-free). At last follow-up, 31.5% had a favorable outcome and 5.2% were seizure free. The only factor significantly predicting favorable outcome was time to vagus nerve stimulator implantation, with the best outcome achieved when vagus nerve stimulator implantation was performed within 3 years of seizure onset. Implantation between 3 and 5 years after epilepsy onset correlated with better long-term seizure freedom (13.3% at T5). Overall, 65.2% of patients evidenced improved quality of life at last follow-up. However, 12.4% had adverse events, but most were mild and disappeared after 3-4 months. **Conclusions:** Early vagus nerve stimulator implantation within 5 years of seizure onset was the only predictor of favorable clinical outcome in pediatric patients. Improved quality of life and a low incidence of significant adverse events were observed.

Keywords

vagus nerve stimulation, drug-resistant childhood epilepsy, outcome predictors.

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Epilepsy is a chronic neurologic disorder affecting approximately 1% of the world's population.[1,2] Despite modern antiepileptic drug treatment, approximately 30% of cases remain medically refractory, and for these patients, surgery is an important treatment consideration.[3] Unfortunately, many drug-resistant cases are ineligible for excisional procedures, and only 50% to 80% of surgical patients achieve long-term seizure freedom[4,5]; therefore, vagus nerve stimulation remains an effective alternative for medically intractable patients who are not candidates for respective surgery.[6]

The efficacy of vagus nerve stimulation therapy in drug-resistant epilepsy was initially demonstrated 2 decades ago. Several studies have confirmed that its efficacy increases over time with an average of 53.53% patients achieving >50% reduction of seizure frequency.[7] However, predicting which

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patients will respond to vagus nerve stimulation treatment remains challenging. The results of several studies analyzing predictors of vagus nerve stimulation efficacy have yielded variable or conflicting results examining the influence of epilepsy duration before implantation, age of seizure onset, or age at vagus nerve stimulator implantation in childhood.[5,8-33]

We herein report a multicenter experience analyzing a large cohort of pediatric patients with medically drug-resistant epilepsy who underwent vagus nerve stimulator implantation. Our aim was to analyze the contribution of factors predicting favorable postsurgical outcome.

Material and Methods

We retrospectively analyzed the medical records of pediatric patients with drug-resistant epilepsy who underwent vagus nerve stimulator implantation at the IRCCS–Institute of Neurological Sciences of Bologna, Sant'Orsola University Hospital in Bologna and Nicklaus Children's Hospital in Miami between 2008 and 2018. We included patients who were 18 years or younger at time of vagus nerve stimulator implantation, and who had at least 1 year of follow-up. Prior to vagus nerve stimulator implantation, all patients underwent a detailed preoperative investigation that excluded the option of resective surgery.

Postoperative vagus nerve stimulation parameters were as follows: current 0.25 mA, frequency 30 Hz, pulse width 500 ms, on-time 30 seconds/off-time 5 minutes. Current settings were gradually increased by 0.25 mA every 1-3 months until patient intolerance, seizure freedom, or a maximum current of 2.5 mA.

Variations to the stimulus parameters in nonresponders were made to obtain a change in response. These attempts were made independently by the treating epileptologist and were based on clinical assessment.

Retrospective clinical information included age at seizure onset, epilepsy duration before vagus nerve stimulator implantation, seizure frequency before implantation, age at vagus nerve stimulator implantation, epilepsy type, brain magnetic resonance imaging (MRI), etiology, number of antiepileptic drugs, adverse events, and quality of life. Vagus nerve stimulation parameter adjustments and modifications of antiepileptic medication were based on clinical decisions by epileptologists at each institution.

Age at seizure onset was subdivided into <1 year, 1-6 years, 6-12 years, and >12 years and age at vagus nerve stimulator implantation into <6 years, 6-12 years, and >12 years. Time to implantation was categorized as <3 years, 3-5 years, and >5 years. Seizure frequency was classified as daily (≥1 seizure per day), weekly (≥4 seizures per month, ≤6 seizures per week), and monthly (≤3 seizures per month). Preimplantation and postimplantation seizure frequency data were retrospectively assessed from the patients' medical records at each Center.

Seizure semiology was classified as generalized (including primary and secondarily generalized tonic-clonic, atonic and absence seizures), focal (with or without impairment of consciousness, included auras), and focal and generalized if both were present. Brain MRI was analyzed and categorized as lesional or nonlesional. The number of the antiepileptic drugs was categorized into 1, 2, or more than 2 drugs.

Based on post–vagus nerve stimulation seizure reduction, patients were classified as nonresponders (≤24% reduction, no change or increased), poor responders (25%-49% reduction) and good responders (≥50% reduction). We defined seizure freedom as complete cessation of all seizures (seizure frequency = 0) at a specified time point.

Outcome was defined as favorable when seizures reduction was >50% at last follow-up. Outcome data were obtained via direct clinical assessment or telephone interview and classified at 1 (T1), 2 (T2), 3 (T3), and 5 (T5) years postimplantation. Data from all telephone interviews were further confirmed in the medical records of the treating epileptologist. New-onset adverse events were reported according to Food and Drug Administration (FDA) criteria.[32] We qualitatively assessed quality of life by questioning the patient or parents about overall quality of life and categorized responses as improved, unchanged, or worse compared to pre–vagus nerve stimulation baseline. Quality of life parameters (alertness, school achievement, mood, seizure intensity, postictal state) were collected by physicians on a voluntary basis using a nonstandardized center questionnaire at follow-up visits.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as absolute and relative frequencies (%).

Fisher exact test was used to evaluate univariate association between overall outcome (T1, T2, T3, and T5) and each individual variable collected including age at epilepsy onset, seizure frequency before and age at implantation, epilepsy duration before implantation, seizure type, brain MRI, etiology, and number of antiepileptic drugs. We also analyzed for any effect based on hospital differences. All P values were based on 2-sided tests with $P < .05$ being significant.

Multiple logistic regression analysis was performed to evaluate the association between timing of vagus nerve stimulator implantation (<5 vs > 5 years) and favorable outcome (>50% seizures reduction) at T1, T2, T3, and T5, adjusted for seizure frequency before implantation at hospital centers. Results are presented as odds ratio (OR) and relative 95% confidence interval (95% CI). Statistical analysis was performed using the statistical package Stata SE, 14.0.

Results

Patients

Eighty-nine patients undergoing left vagus nerve stimulator implantation for intractable epilepsy met inclusion criteria. All underwent a comprehensive presurgical evaluation that had excluded the possibility of performing an excisional surgical procedure. No patient had prior surgery. Mean age at vagus nerve stimulator implantation was 12 years 7 months (range 15 months–18 years), and mean age at seizure onset was 3 ½ years. Table 1 summarizes the population parameters at baseline.

Among 49 patients (55%) showing structural epilepsy, 41 (83.6%) were due to cortical malformation, 5 (10.2%) to perinatal hypoxic-ischemic brain injury, and 4 (6.2%) to infection.

Patient attrition over time resulted in a population of 86 patients at T2, 84 at T3, and 57 at T5. Three patients switched off their vagus nerve stimulator because of increased seizure frequency (at T1), and 2 subjects dropped out because of no

Table 1. Clinic and Demographic Population Characteristics at 1 Year of Follow-up.

Age at seizure onset, y	n (%)	Antiepileptic drugs	n (%)
<6	66 (74.2)	1	5 (5.6)
6-12	19 (21.3)	2	27 (30.3)
>12	4 (4.5)	>2	57 (64.1)
Timing of VNS implantation, y		Age at VNS implantation, y	
<3	8 (9.0)	<6	12 (13.5)
3-5	22 (24.7)	6-12	27 (30.3)
>5	59 (66.3)	>12	50 (56.2)
Seizure frequency		Etiology	
Daily	59 (66.3)	Structural and genetic	3 (3.4)
Weekly	19 (21.3)	Structural	49 (55.0)
Monthly	11 (12.4)	Genetic	9 (10.2)
		Unknown	28 (31.4)
Seizure type		Brain MRI	
Focal	41 (46.1)	Lesional	52 (58.4)
Generalized	28 (31.4)	Nonlesional	37 (41.6)
Focal and generalized	20 (22.5)		

Abbreviations: MRI, magnetic resonance imaging; VNS, vagus nerve stimulation.

benefit (at T3). Remaining patients had a follow-up less than 5 years.

Throughout the follow-up period, the median pulse width and frequency remained unchanged at 500 ms and 30 Hz. The mean output current was stable at 1.8 mA from 1 to 5 years.

Seizure Outcome

Figure 1 presents the results of vagus nerve stimulation efficacy. The responder rate (seizure frequency reduction > 50%) at 1-year follow-up was 25.8%, with 4.5% achieving seizure freedom; at last follow-up, there were 31.5% responders, with 5.2% achieving seizure freedom. Table 1 summarizes the demographic and clinical characteristics at 1 year of follow-up: age at epilepsy onset, seizure frequency pre-implantation, age at vagus nerve stimulator implantation, time to implantation, seizure type, brain MRI, etiology, number of antiepileptic drugs.

The only prognostic factor that correlated significantly with favorable seizure outcome was time to vagus nerve stimulator implantation, with the best overall outcome achieved in patients implanted within 3 years of seizure onset. Negative linear impairment in outcome correlated with implantation after 3-5 years. Seizure outcome was even less successful if performed after 5 years from seizure onset.

Table 2 reveals that the majority of patients evidenced a >50% reduction in seizure frequency when vagus nerve stimulator implantation was performed < 3 years from seizure onset. When time to implantation increased to 3-5 years, seizure reduction dropped to 25%-49%, and further decreased to <24% at >5 years.

Time to implantation of 3-5 years was also the best predictor of better outcome, with responder rates of 9.1% at T1 and 13.3% at T5. The best long-term outcome was obtained when time to implantation was <5 years, with the majority of patients

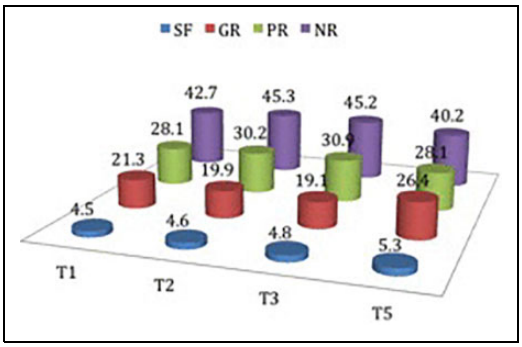

Figure 1. Vagus nerve stimulation efficacy during overall follow-up. NR, non responders; PR, poor responders; GR, good responders; SF, seizure free; T1, 1-year follow-up; T2, 2-year follow-up; T3, 3-year follow-up; T5, 5-year follow-up.

showing seizure reduction >50%, and 13.3% achieving seizure freedom.

Multiple logistic regression analysis revealed that time to vagus nerve stimulator implantation was the main predictor of response to vagus nerve stimulation and was not influenced by any of the other variables. We also excluded any possible influence conferred by the hospital where the implantation was performed, by comparing the results obtained in the individual centers.

Table 3 summarizes the statistical data assessing the correlation of seizure frequency reduction to other parameters.

OR adjusted was, respectively, 2.9 (95% CI 1.1-8.2) at T1, 5.2 (95% CI 1.7-15.6) at T2, 3.3 (95% CI 1.1-9.9), at T3 and 4.6 (95% CI 1.4-15.9) at T5.

Overall, 65.2% of patients experienced improved quality of life at last follow-up; no meaningful changes during overall follow-up were noted (Table 4). Eleven patients (12.4%) experienced an adverse event, including increased seizure frequency (n = 3), cough (n = 3), hoarseness (n = 3),

Table 2. Correlation Between Seizure Outcome and Timing of Implantation.

	Follow-up 1 y, % (n = 89 patients)				Follow-up 2 y, % (n = 86 patients)				Follow-up 3 y, % (n = 84 patients)				Follow-up 5 y, % (n = 57 patients)			
Timing	≤24	25-49	≥50	SF	≤24	25-49	≥50	SF	≤24	25-49	≥50	SF	≤24	25-49	≥50	SF
<3 y	12.5	12.5	62.5[a]	–	14.3	28.6	57.1[a]	–	33.3	16.7	50.0[a]	–	33.3	16.7	50.0[a]	–
3-5 y	9.1	59.1[a]	22.7	9.1	9.1	50.0[a]	31.8	9.1	18.2	45.4[a]	27.3	9.1	6.7	40.0[a]	40.0	13.3
>5 y	59.3[a]	18.6	15.3	3.4	63.2[a]	22.8	10.5	3.5	57.1[a]	26.8	12.5	3.6	55.6[a]	24.9	16.7	2.8
P value[b]			**<.001**				**<.001**				**<.01**				**<.01**	
											>.001				**>.001**	

Abbreviations: SF, seizure free (Fisher exact test); –, no patients.
[a]Values underline the reduction of the responder rate with the increase in implantation timing included at every follow-up.
[b]*P* value refers to those significant results noted when the timing of the vagus nerve stimulator implantation was less than 3 years from epilepsy onset.

Table 3. Statistical Data (Fisher Exact Test) on the Correlation of Seizures Frequency Reduction With Other Parameters Analyzed.

Other parameters	*P* value
Age at seizure onset	*1.000*
Seizure frequency	*.935*
Seizure type	*.210*
Antiepileptic drugs	*1.000*
Age at vagus nerve stimulator implantation	*.430*
Etiology	*>.99*

Table 4. Adverse Events and Quality of Life.

Adverse events	n (%)
No	78 (87.6)
Yes	11 (12.4)
Seizure increase	3/89 (3.4)
Cough	4/89 (4.5)
Hoarseness	2/89 (2.3)
Dysphagia	1/89 (1.1)
Pharyngodynia	1/89 (1.1)
Quality of life	Last follow-up
Unchanged	31 (34.8)
Improvement	58 (65.2)

dysphagia (n = 1), and pharyngodynia (n = 1) (Table 4). Three patients with an increased seizure frequency exited the study at T1. Adverse events in the remaining cases were mild and disappeared within 3-4 months following surgery.

Discussion

Previous studies of prognostic factors of seizure outcome after vagus nerve stimulator implantation were conducted on combined populations of adult and pediatric patients. These studies typically included wide-ranging implantation ages, and did not examine prognostic factors exclusively in a pediatric population.[8-33] Moreover, the results of previous studies were variable, yielding conflicting descriptions of epilepsy duration before vagus nerve stimulator implantation.[7]

We found overall responder rates at follow-up ranging from 25.8% at T1 (4.5% seizure-free) to 31.5% at T5 (5.2% seizure-free). The overall responder rate was lower than the average of the results reported in previous studies (range 12.7%-73.2%, average: 53.3%),[4] but most of our patients and their caregivers (65.2%) indicated an improvement in quality of life during follow-up visits. Improved quality of life was related to positive clinical effects apart from seizure reduction, including alertness, school achievement, mood, seizure intensity, and postictal state, as described by several authors.[16]

Despite lower seizure response rates in our patients, our study is the first to employ a population where age of seizure onset and vagus nerve stimulator implantation occurred in childhood. Our responder rates are therefore not directly comparable to previous published studies.

We found that early vagus nerve stimulator implantation is the only long-term positive predictor of response to the neurostimulation in childhood-onset drug-resistant epilepsy. In particular, we showed that vagus nerve stimulator implantation within 3 years of seizure onset predicted a more favorable seizure outcome, in conjunction with increasingly less favorable outcomes when implantations were performed between 3 and 5 years. However, although time to implantation <3 years was optimal for seizure frequency reduction, a 3-5-year time frame was associated with superior seizure freedom, indicating that favorable long-term seizure outcomes continue within a 5-year window after implantation (seizure reduction >50%, 13.3% seizure freedom). Multiple logistic regression analysis further underscored the importance of time to vagus nerve stimulator implantation as there was no significant influence by other variables. Intervention in early life during brain maturation would be expected to help prevent the encephalopathic effects of epilepsy and likely establishment of aberrant circuits. Vagus nerve stimulation–induced seizure reduction or seizure freedom during this critical period favors positive neurophysiological modulations and potential changes in brain blood flow and brain neurotransmitter metabolism that could modulate neuronal excitability, induce long-lasting changes in neuronal network formation, and ultimately lead to an improved quality of life.

In only 1 study it was hypothesized that earlier nonpharmacologic treatment using vagus nerve stimulation therapy in

patients with medically refractory seizures would be more efficacious than later adjunctive use of vagus nerve stimulation therapy, but follow-up was only 3 months.[27] Therefore, early vagus nerve stimulator implantation should be considered as soon as the clinical characteristics of the epilepsy indicate refractoriness, with a goal of decreasing seizure burden over time.[34]

The high tolerability of vagus nerve stimulation therapy, with 12.4% of patients reporting only minor adverse events, attests to the clinical utility of vagus nerve stimulator implantation. Most patients (75%) reported only mild adverse effects, and the majority of these effects disappeared by the third or fourth postoperative month. This further supports the positive risk-benefit ratio associated with earlier vagus nerve stimulation intervention.

The most important limitation of our study is its retrospective structure and lack of a control group. The variable seizure etiologies might be considered another limitation, but the absence of different responsiveness for different seizure types suggest that this limitation is unlikely to influence the prognostic importance of time to surgery.

Alternatively, a retrospective study has the advantage that results cannot be predetermined, evaluations are based on existing data sources in which both exposure and outcomes are readily available and the results cannot be tailored to the collection of data for a specific therapy. Furthermore, our findings confirm the long-term efficacy and safety of vagus nerve stimulation in children with drug-resistant epilepsy and reveal that early vagus nerve stimulator implantation is the main predictive factor of favorable outcome.

Conclusion

This study confirms the importance of early vagus nerve stimulation to treat childhood-onset drug-resistant epilepsy, especially within 5 years of seizure onset. Earlier intervention was the only predictor of favorable clinical outcome as all other variables including age at epilepsy onset, seizure frequency, age at vagus nerve stimulator implantation, seizure type, brain MRI, the number of antiepileptic drugs, and treatment location were not significant. Improved quality of life and a minor adverse event profile were noted. Vagus nerve stimulator implantation should be considered when the electroclinical data reveal refractory epilepsy and the role of excisional surgery is excluded.

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Author Contributions

AR contributed to study conception and design and to acquisition, analysis, and interpretation of the data and wrote the article. AH, VG, and DC contributed to data acquisition, analysis, and interpretation. AP, DMC, PJ, TM, IM, MZ, ML, JR, and TR drafted the manuscript. MD critically revised the manuscript and gave final approval. All authors contributed to, read, and gave final approval.

Declaration of Conflicting Interests

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Ethical Approval

Database analyses were conducted in accordance with institutionally human subject protection protocols.

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