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Early vagus nerve stimulator implantation as a main predictor of positive outcome in pediatric patients with epileptic encephalopathy

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ABSTRACT

Objective. We describe a multicenter experience with VNS implantation in pediatric patients with epileptic encephalopathy. Our goal was to assess VNS efficacy and identify potential predictors of favorable outcome.

Methods. This was a retrospective study. Inclusion criteria were: ≤18 years at the time of VNS implantation and at least one year of follow-up. All patients were non-candidates for excisional procedures. Favorable clinical outcome and effective VNS therapy were defined as seizure reduction >50%. Outcome data were reviewed at one, two, three and five years after VNS implantation. Fisher's exact test, Kaplan-Meier and multiple logistic regression analysis were employed.

Results. Twenty-seven patients met inclusion criteria. Responder rate (seizure frequency reduction ≥ 50%) at one-year follow-up was 25.9%, and 15.3% at last follow-up visit. The only variable significantly predicting favorable outcome was time to VNS implantation, with the best outcome achieved when VNS implantation was performed within five years of seizure onset (overall response rate of 83.3% at one year of follow-up and 100% at five years). In total, 63% of patients evidenced improved QOL at last follow-up visit. Only one patient exited the study due to an adverse event at two years from implantation.

Significance. Early VNS implantation within five years of seizure onset was the only predictor of favorable clinical outcome in pediatric patients with epileptic encephalopathy. Improved QOL and a very low incidence of adverse events were observed.

Key words: vagus nerve stimulation; epileptic encephalopathies; outcome predictors

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Epilepsy is a common neurological disorder in childhood with a prevalence of approximately 0.5% [1].

Among the various presentations of childhood epilepsy, the epileptic encephalopathies represent an important group with severe and drug-resistant epileptic seizures, early onset and poor developmental outcome.

According to the International League Against Epilepsy, "epileptic encephalopathies" are defined as conditions in which " the epileptic activity itself may contribute to severe cognitive and

behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation), and that these can worsen over time" [2]. In some cases, developmental slowing emerges before the onset of frequent epileptic activity on EEG; in these cases the suggested term is "developmental and epileptic encephalopathies" [2].
VNS remains an effective adjunctive treatment for medically intractable patients who are not candidates for resective surgery [3], however, predicting which patients will respond to VNS treatment remains challenging. Several published studies suggest possible benefits of VNS in patients with drug-resistant seizures, including "*epileptic encephalopathies*" such as Lennox-Gastaut syndrome or "*developmental and epileptic encephalopathies*" such as Dravet syndrome [4-13], but no studies have analyzed the factors predicting favorable outcome.
We herein report a multicenter experience with a cohort of pediatric patients with epileptic encephalopathies who underwent VNS implantation in order to examine the contribution of factors predicting favorable post-surgical outcome.

Material and methods

We retrospectively analyzed the clinical records of pediatric patients with "epileptic encephalopathy" and "developmental and epileptic encephalopathy" undergoing VNS implantation at the IRCCS - Institute of Neurological Sciences and Sant' Orsola University Hospital in Bologna, and Nicklaus Children's Hospital, Miami between 2008 and 2018.
All patients were considered as a single group of epileptic encephalopathies (EE) for study purposes; the clinical features of this population are shown in *table 1*.
We included patients younger than 18 years at the time of VNS implantation who had at least one year of follow-up. Prior to VNS implantation, all patients were found to be non-candidates for epilepsy surgery.
Post-operative VNS stimulation parameters were: current of 0.25 mA, frequency of 30 Hz, pulse width of 500 ms, and on-time of 30 seconds/off-time of 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. Stimulus parameters were modified qualitatively in non-responders to improve responsivity. All modifications were made independently by the treating epileptologist based on clinical assessment.
Clinical variables examined retrospectively included epilepsy onset, epilepsy duration before the VNS (time to VNS implantation), seizure frequency and age at VNS implantation, type of epilepsy, etiology, MRI findings, number of antiepileptic drugs, adverse events and QOL.
VNS stimulation parameters and antiepileptic drugs were determined independently by epileptologists at each institution.
Age at epilepsy onset was further classified into: <one year and <three years; age at VNS implantation was divided into: <6 years, 6-12 years and >12 years. Time to implantation was classified as < five years and > five years from seizure onset.
Seizure frequency was classified as daily (≥ one seizure per day) and weekly (≥ four seizures per month, ≤six seizures per week). Pre-implantation and post-implantation seizure frequency data was retrospectively assessed from patient medical records at each center.
The clinical practice of each seizure unit involved in this study requires careful collection of the clinical data, such as frequency, duration and semiological features of the seizures. Seizures were classified

▼ **Table 1.** Clinical and demographic population characteristics.

Age at seizure onset	
< 1 years	16 (59.2%)
< 3 years	11 (40.8%)
Timing of VNS implantation	
< 5 years	6 (22.2%)
> 5 years	21 (77.8%)
Seizure frequency	
Daily	18 (66.7%)
Weekly	9 (33.3%)
Epileptic syndromes	
Lennox-Gastaut	7 (25.9%)
Dravet	4 (14.8%)
Undefined	16 (59.3%)
Antiepileptic drugs	
2	4 (14.8%)
> 2	23 (85.2%)
Age at VNS implantation	
< 6 years	5 (18.5%)
6-12 years	12 (44.4%)
> 12 years	10 (37.1%)
Etiology	
Structural	11 (40.7%)
Genetic	7 (25.9%)
Structural and genetic	1 (3.8%)
Unknown	8 (29.6%)
Brain MRI	
Lesional	12 (44.4%)
Negative	15 (55.6%)

according to the International League Against Epilepsy classification [14]. Brain MRI was categorized as lesional or negative (normal or non-localizing). The number of antiepileptic drugs was divided into two or more than two drugs. No patients were being treated with monotherapy.

Based on post-VNS seizure reduction, patients were designated as non-responders (reduction ≤24%, no change or increase), poor responders (25-49% reduction) and good responders (reduction ≥50%). Freedom from epileptic seizures (SF) was defined as the complete cessation of all seizures (seizure frequency = 0) at the time of a follow-up visit.

Patients were defined as seizure-free if the last seizure occurred at least six months before the follow-up visit.

The outcome was considered "favorable" when seizure reduction was > 50% at the last follow-up visit.

Outcome data were recorded through direct clinical evaluation or telephone interview and classified at one (T1), two (T2), three (T3) and five (T5) years after VNS implantation.

Quality of life (QOL) data, retrospectively collected, was obtained by questioning the caregivers about overall lifestyle, and results were designated as improved, unchanged or worse relative to pre-VNS implantation. QOL parameters (vigilance, behavior, seizure intensity, post-ictal status) were collected using assessment questionnaires at each follow-up visit. QOL parameters also included "caregiver QOL" due to the potential for emotional fatigue accompanying the management of patients with EE.

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

Statistical analysis

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

Fisher's exact test was used to evaluate the association between overall outcome (T1, T2, T3 and T5) and each individual variable collected including age at epilepsy onset, duration of epilepsy, seizure frequency before VNS implantation, age at implantation, time to implantation, seizure type, brain MRI, etiology, number of antiepileptic drugs and hospital center. All *p* values were based on 2-sided tests with $p < 0.05$ being significant.

Time to first best response (Kaplan-Meier analysis) was considered the end point for the survival analysis, and univariate hazard ratios (HR), with 95% confidence interval (95% CI), were computed to find end-point-related prognostic factors.

Multiple logistic regression analysis was performed to evaluate the association between timing of VNS implantation (< 5 vs. > 5 years) and favorable outcome (> 50% seizure reduction) at T1, adjusted for other variables. Likelihood-ratio test was used to evaluate the best prediction model. Results are presented as odds ratio (OR) and relative 95% confidence interval (95% CI)

Statistical analysis was performed using statistical package Stata SE, 14.2.

Results

Patients

Twenty-seven patients undergoing left VNS implantation for EE met the inclusion criteria. Mean age at VNS implantation was 10 years and three months (range: 4-18 years), and mean age at seizure onset was one year and two months. *Table 1* summarizes the population parameters at baseline.

Patient attrition over time resulted in a population of 27 patients at T1, 26 patients at T2, 25 at T3, and 13 at T5. Among patients lost during the follow-up, one patient switched off his VNS because of increased seizure frequency (at T2) and one patient dropped out because of no benefit (at T3). The remaining patients had follow-ups of less than five years.

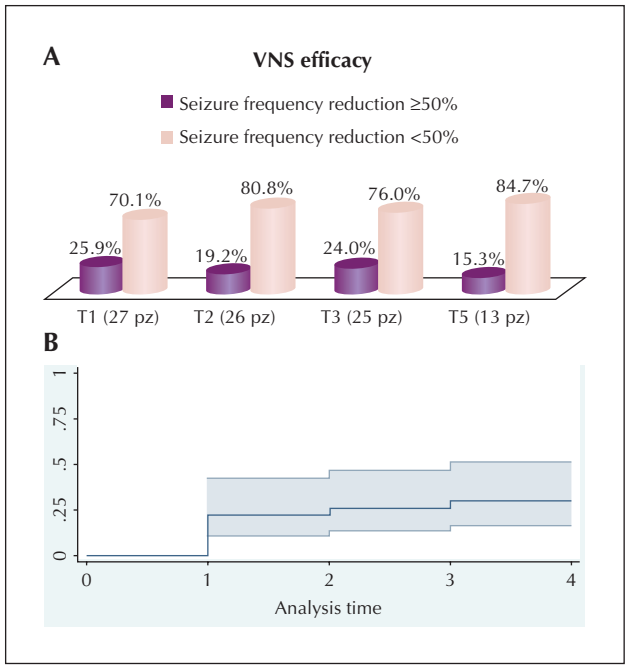
Throughout the follow-up period, median pulse width and frequency remained unchanged at 500 ls and 30 Hz, respectively. The mean output current stabilized at 1.8 mA from one to five years.

Seizure outcome

VNS efficacy results are presented in *figure 1A*. The responder rate (seizure frequency reduction ≥ 50%) after one year of follow-up was 25.9%; at the last follow-up visit, there were 15.3% responders. Kaplan-Meier analysis revealed that the time to first best response from VNS implantation was one year (*figure 1B*). The subsequent trajectory followed a more constant growth trend.

The association between outcome and time of VNS implantation (< five vs. > five years) at the four time points (T1, T2, T3 and T5) is presented in *table 2*.

Multiple logistic regression analysis revealed that time to VNS implantation was the main predictor of response to VNS at one year from implantation (O =47.5; 95% CI: 10.4-217.8). This strong prediction was not influenced by any other variable (age at epilepsy onset, seizure frequency pre-implantation, age at VNS implantation, time to implantation, epilepsy type,



■ **Figure 1.** (A) VNS efficacy during overall follow-up. T1: one year of follow-up; T2: two years of follow-up; T3: three years of follow-up; T5: five years of follow-up; pz: patients. (B) Time to first best response (Kaplan-Meier analysis): the time to first best response was one year from VNS implantation.

brain MRI, etiology, number of antiepileptic drugs), including the hospital where the implantation was performed (*table 2*).
These results are summarized in *figure 2A*; the only prognostic factor that correlated significantly with favorable seizure outcome was "time to VNS implantation", and at each follow-up interval, the majority of patients evidenced a >50% reduction in seizure frequency when VNS implantation was performed < five years from seizure onset.

These results were further emphasized based on the Kaplan-Meier analysis, as shown in *figure 2B*. Data analysis revealed that time to VNS implantation <five years compared to >five years increased the probability of a 15-fold greater frequency reduction (HR=15.9; 95% CI: 3.9-64.7).
In total, 63% of patients experienced improved QOL at the last follow-up visit; no meaningful changes during overall follow-up were noted (*table 3*). Two patients (7.4%) experienced adverse events- increased seizure frequency (*n*=1) and cough (*n*=1). One patient with increased seizure frequency exited the study at T2. Adverse events in the remaining case were mild and disappeared within three to four months of implantation.
Finally, patients with early VNS implants also showed improvement in their background activity and interictal abnormalities on follow-up EEG.
No substantial difference was found in outcome data from patients with Lennox-Gastaut syndrome, Dravet syndrome or EE.

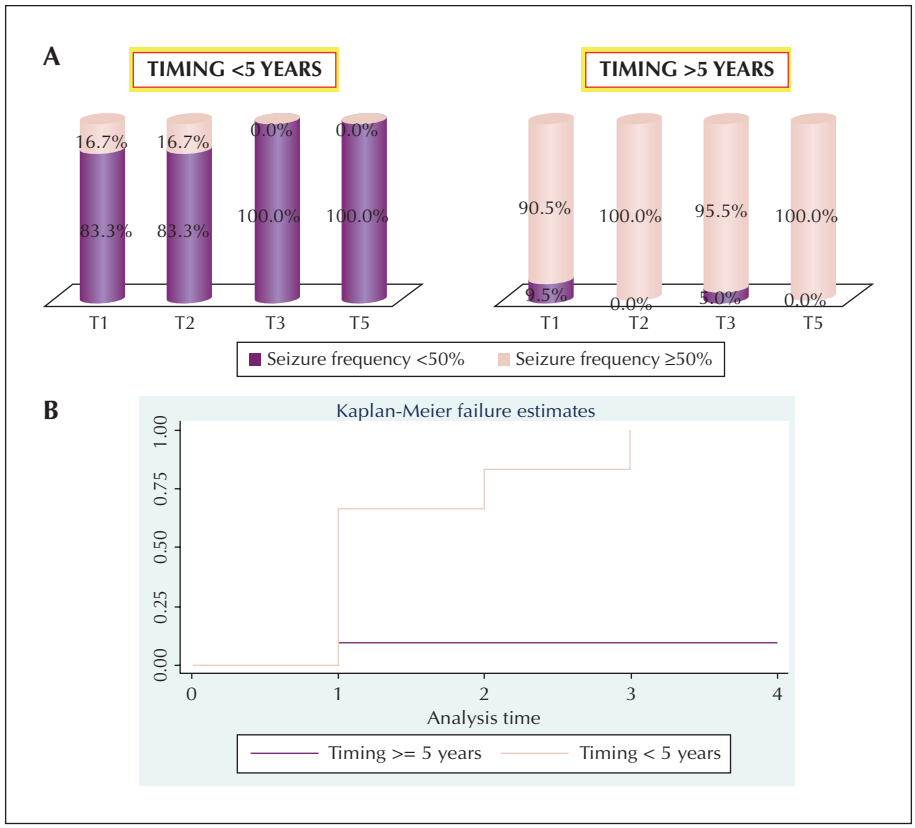
Discussion

Pilot studies of vagus stimulation for patients with drug-resistant focal epilepsy reported average reductions in seizure frequency of 47% and ≥50% after one to three years [15]. More recently, >50% reductions in seizure frequency were reported in approximately 60% of implanted patients [16,17].
Similar findings were observed in children with average reduction in seizure frequency of between 50% and 55% after follow-ups ranging from three to 10 years [18-23]. VNS in pediatric age reduced sudden death in children with drug-resistant epilepsy [24] and was not associated with an increase in adverse events compared to adults [25].
Predicting response to VNS remains challenging as most studies are inhomogeneous for seizure type and patient age, and prognostic factors are analyzed only after VNS implantation [12,21,26-49].

▼ **Table 2.** Correlation between overall outcome and timing of implantation.

	Follow-up 1 yr		Follow-up 2 yrs		Follow-up 3 yrs		Follow-up 5 yrs	
Timing	SF< 50%	SF≥ 50%	SF< 50%	SF≥ 50%	SF< 50%	SF≥ 50%	SF< 50%	SF≥ 50%
< 5 years	16.7%	83.33%	16.7%	83.3%	0%	100%	0%	100%
> 5 years	90.5%	9.5%	100%	0%	95.0%	5.0%	100%	0%
		$p < 0.001$		$p < 0.001$		$p < 0.001$		$p < 0.001$

SF: seizure frequency.



■ **Figure 2.** (A) Comparison of VNS efficacy between time of implantation <five years and >five years from seizure onset. TIMING < 5 YEARS: VNS implantation <five years to seizure onset; TIMING >5 YEARS: VNS implantation >five years to seizure onset; T1: one year of follow-up; T2: two years of follow-up; T3: three years of follow-up; T5: five years of follow-up. (B) Time to first best response (Kaplan-Meier analysis) between the time of VNS implantation <five years and >five years; time to VNS implantation <five years compared to >five years increases the probability of a 15-fold greater reduction in frequency.

This study reveals that the only significant factor predicting favorable outcome in pediatric patients with EE was time to VNS implantation, with the best outcome achieved when VNS implantation was performed within three years of seizure onset. Furthermore, implantation between three and five years after epilepsy onset in this population also correlated with improved long-term seizure freedom (13.3% at five years of follow-up); 65.2% of improved patients also evidenced an improved QOL at the last follow-up visit.

There is little information on the efficacy of VNS in EE as most studies focus on patients with Lennox-Gastaut and Dravet syndromes (the latter currently defined as a developmental and epileptic encephalopathy), revealing a >50% reduction in seizure frequency in 30-50% of patients, associated with a favorable QOL [5,8,11,13,14,50-53]. We found an overall response rate of 25.9% at one year of follow-up and 15.3% at five years (*figure 1A*), with the best response (Kaplan-Meier analysis) one year after VNS implantation (*figure 1B*).

The overall VNS response diminished over time, but in our population, the six patients implanted at between three and five years after seizure onset achieved a five-year follow-up response rate of ≥50%, underlining the positive predictive value of early VNS implantation compared to late implantation. Furthermore, the six patients with early VNS implantation were also younger than those with late implantation which confirmed the data showing that younger patients may be better VNS responders [42]. Most of our patients and their caregivers (63%) reported an improved QOL that began in the first year after VNS implantation and increased in subsequent years. The improved QOL was not limited to a reduction of seizure frequency as vigilance, behavior, seizure intensity and post-ictal status also improved.

No reported studies analyzed for predictors of favorable outcome in EE after VNS implantation. Our study

shows that early VNS implantation was the single most important long-term predictor of responsiveness in EE. We demonstrate that VNS implantation within five years of seizure onset was associated with a more favorable overall response rate; 83.3% at one year of follow-up and 100% at five years, compared to unfavorable results for implants performed after five years (response rate of 9.5% at one year and 0% at five years of follow-up) (*figure 2A*). Kaplan-Meier analysis reaffirmed that time to first best response at one year of follow-up was strictly dependent on early VNS implantation (*figure 2B*).

Comparing *figure 1* to *figure 2* further reveals that early VNS implantation in patients with EE leads to a positive outcome. Multiple logistic regression analysis underscored the importance of timing of VNS implantation as no other variables influenced seizure outcome. There were no substantial differences among patients with Lennox-Gastaut syndrome, Dravet syndrome or non-syndromic EE.

Intervention in early life during brain maturation would be expected to help prevent the encephalopathic effects of epilepsy and likely establishment of aberrant circuits. This concept would lead to effects that are most apparent in very young children who have greater brain plasticity, and for the epileptic encephalopathies, for which, by definition "*the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation), and that worsen over time*" [2]. Kaplan-Meier analysis reaffirmed that time to first best response at one year of follow-up was strictly dependent on early VNS implantation". Kaplan-Meier analysis reinforced these concepts and emphasized the importance of early VNS implantation to achieve optimal one-year follow-up.

It is currently well known that brain networks are organized in small-worldness and modularity [54,55]. This organization is altered in neurological disorders, including epilepsy, a disease involving a global disorder of brain dynamics with pathological functional and structural connectivity [56-60]. Furthermore, it has also been reported that the alteration of brain network functional topology in epilepsy is related to vulnerability to seizures, and that network organization is less efficient interictally [59-67]. These observations are consistent with the theory that epilepsy is a network disorder and that the seizures occur due to an anomalous topology of structural and functional networks [68-70]. It is well known that network features depend on the size of the network and connection density [71,72].

Recent studies have shown that VNS induces integrated network organization (smaller diameter and eccentricity), a more balanced topology (higher hierarchy: no overload of the central nodes) and less pathological architecture (higher leaf fraction) [73]. VNS treatment leads to more efficient reorganization of functional brain networks (*i.e.* more integrated) and network structure, and these changes correlate with clinical improvement [73].

Based on these observations, we speculate that early intervention leads to a widespread reorganization of brain networks and impedes the establishment of aberrant circuits linked to the encephalopathic state. These changes may also influence complex processes determining drug resistance and the semiological variability of seizures in epileptic encephalopathies.

The hypothesized large-scale reorganization of brain networks may also explain why VNS not only affects epilepsy but also modifies cognitive and behavioral functions [74].

Reduction of seizure frequency during the critical period of maturation would be expected to reduce, if not prevent, long-lasting changes in neuronal network formation, leading to clinical improvement and improved QOL. The overall clinical improvement that we found in patients with EE was accompanied by improved caregiver QOL, a result that potentially also reduces caregiver burnout and favors a more positive patient-caregiver interaction.

Our data therefore suggest that earlier VNS implantation should be considered in EE with the aim of reducing seizure frequency. Our clinical results are supported by the improved background and interictal activity on EEG after early VNS implantation. Without studies that carefully analyze changes on EEG background activity after VNS implantation, we cannot exclude the possibility that EEG background features could improve through brain maturation alone, particularly in early life. Only further investigation into the direct effects of early VNS implantation on EEG will resolve this issue.

Finally, our study confirms the high tolerability of VNS therapy in very young patients with only one drop-out due to an adverse event (increased seizure frequency), two years after implantation. It is important

▼ **Table 3.** Adverse events and QOL data.

Adverse events	
No	25 (92.6%)
Yes	2 (7.4%)
Seizures increased	1/27 (3.7%) dropped out at T2
Cough	1/27 (3.7%)
Quality of life (at last follow-up visit)	
Unchanged	10 (37%)
Improvement	17 (63%)

to emphasize that increased seizures, two years after implantation, may not necessarily be related to VNS given the unpredictable natural course of EE (*table 3*). The most important limitation of our study is its retrospective methodology and lack of a control group. However, an advantage of retrospective studies is that results are not predetermined, as all evaluations are based on existing data sources in which both exposure and outcomes are readily available. Furthermore, the results cannot be tailored to the collection of data for a specific therapy. Our study was conducted before the VNS Autostim feature was introduced which may have contributed to the low observed responder rate. In conclusion, this study confirms the importance of early VNS to treat EE, especially within five years of seizure onset, as this variable is the only significant predictor of favorable clinical outcome. Improved QOL and a minor adverse event profile were noted. VNS implantation should be considered as soon as the electroclinical data reveals EE. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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TEST YOURSELF

(1) What is the main predictor of positive outcome after VNS implantation in patients with epileptic encephalopathies?

(2) Why should the timing of VNS implantation be important in epileptic encephalopathies?

(3) What could be the mechanism by which VNS acts on the organization of brain networks?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".