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Vagus Nerve Stimulation for Children with Drug-resistant Epilepsy: Evidence from Routine Clinical Practice

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Abstract

Objective: Vagus nerve stimulation is a well-established adjunctive therapy, despite variability in its efficacy in children with drug-resistant epilepsy. In a tertiary center, it offers a non-resective therapeutic alternative for children to lessen seizure burden and enhance quality of life. Bearing in mind of these considerations, we evaluated the experience of a single-center practice.

Methods: A retrospective observational study was carried out at Children Welfare Teaching Hospital, Epilepsy Clinic. The study reviewed medical records of children with drug-resistant epilepsy who underwent vagus nerve stimulation implantation. The data extracted from January 2025 to January 2026, baseline characteristics, epilepsy etiology, and vagus nerve stimulation programming parameters were analyzed.

Results: The cohort of 36 children diagnosed with drug-resistant epilepsy had a mean age of 6.89±3.62 years at vagus nerve stimulation implantation, with a mean epilepsy period before implantation of 5.03±2.73 years. There was a high median baseline seizure frequency 80 (60-197). Among epilepsy etiologies, genetic causes were identified in 15 of 36 patients. During the study period, none of the vagus nerve stimulation parameters adjustment demonstrated a statistically significant association with response, yet non-responders tended to reach therapeutic stimulation current slightly later than responders.

Conclusion: Vagus nerve stimulation therapy was associated with a lessening in seizure occurrence in a subset of children with drug-resistant epilepsy, among the evaluated titration programs, a shorter time to reach the therapeutic current was associated with clinical response.

Keywords: Drug-resistant epilepsy, neuromodulation, pediatric epilepsy, vagus nerve stimulation

INTRODUCTION

Despite advances in antiseizure medications, seizures remain unresponsive to treatment in a substantial proportion of patients.[1] Epidemiological data indicate that epilepsy remains uncontrolled in approximately one-third of adults[2] and 25% of children with available medications.[3,4] The International League Against Epilepsy defines drug-resistant epilepsy (DRE) as the failure to achieve seizure freedom despite sufficient trials of two suitable and tolerated seizure medications, whether as alone or with other medications.[5] The chance of achieving seizure freedom with subsequent anti-seizure drugs decreases a lot, often falling within the range of 5% to 10%.[6] DRE has several problems, including. Learning and development problems in children, an increased the threat of sudden unexpected death in epilepsy,[7] increased risk of emotional and behavioral problems,[8] and the side effects from multiple antiseizure medications.[9] In DRE, treatment options alternative to medications including surgical removal of the seizure-causing brain part.[10] Less invasive surgical methods including vagus nerve stimulation (VNS). VNS therapy involves implantation of a programmable pulse generator in a subcutaneous pocket in the left anterior chest wall and placement of a helical electrode tunneled subcutaneously and wrapped around the left cervical vagus nerve. Left-sided implantation is routinely performed to minimize potential cardiac effects associated with right Vagus stimulation.[11,12] The clinical efficacy of VNS emerges gradually. Within the first few months of therapy, approximately 40-49% of patients reach a ≥50% reduction in frequency of seizure.[13] The present study provides insight into the local practice at the VNS/epilepsy clinic.

METHODS

Study Design

This observational cohort study was conducted at the epilepsy clinic of the Children Welfare Teaching Hospital, a tertiary pediatric referral center in Baghdad, Iraq. The clinic has been operational since its establishment in 2022. This retrospective study reviewed children who had VNS implantation, programming by three pediatric neurologists in the mentioned clinic since its founding. Ethical approval was obtained in November 2024, and data was extracted from medical records from January 2025 to January 2026. Clinical follow-up duration for each patient was measured individually from date of implantation to the last documented follow-up visit. Among the 36 patients evaluated in our clinic, five patients were excluded from the study: four patients referred from other centers and their baseline data were incomplete in addition to one patient with follow-up duration less than six months. At the time of data extraction, not all patients had completed the planned follow-up duration. Therefore, analysis was involved only patients who reached that timepoint (31 patients reached the current of 1.5mA, of whom 24 patients complete 1 year follow up, and 18 children had VNS implantation for more than 1 year.No data imputation was performed (Figure 1).

Participants

Children were entitled to inclusion if they: 1) Underwent VNS implantation, programming, and follow-up at the VNS clinic for at least 6 months; 2) Had complete baseline clinical data, including seizure frequency; 3) Reaching a current level of 1.5 mA during follow-up.[14]

Outcome Assessment

VNS responsiveness was defined as a reduction of seizure frequency ≥50% in comparison to the baseline. Response status was assessed at three predefined time points: 1) At attainment of 1.5mA current; 2) At 1-year follow-up; and 3) At >1 year of follow-up.

$$\%\ \text{seizure reduction} = \frac{\text{Baseline seizure frequency} - \text{Follow-up seizure frequency}}{\text{Baseline seizure frequency}} \times 100$$

Data Collection

Clinical and device-related data were extracted from medical records and seizure diaries or caregiver reports. Variables included age, sex, onset of epilepsy, epilepsy duration before implantation, age at VNS implantation, seizure frequency as the sum of all seizure types was calculated from the reported seizure number per month or estimated from an average daily seizure frequency when seizure occurred very repeatedly by parental reports. The etiologies of epilepsy were classified based on clinical, radiological, and genetic data. Epilepsy etiologies were classified into 1) Structural: defined when neuroimaging demonstrated a structural brain abnormality. Lesions that were considered relevant if with anatomical location corresponded with seizure semiology and were located in regions known to be epileptogenic, such as cortical or cortico-subcortical areas.[15] 2) Genetic etiology (probable/confirmed): assigned when a genetic variant was identified, or a positive family history of epilepsy or the presence of dysmorphic features or syndromic characteristics were found. 3) Mixed etiology: applied to patients in whom both structural abnormalities and genetic factors were identified and considered contributory to epilepsy. 4) Unknown etiology: used when no clear structural, genetic, infectious, autoimmune, or metabolic cause could be identified despite available investigations. VNS programming parameters recorded during follow-up included output current (mA) and duty cycle.

MAIN POINTS

- Vagus nerve stimulation is effective in pediatric drug-resistant epilepsy, achieving significant seizure reduction across diverse epilepsy etiologies.
- Epilepsy onset, duration, and etiology were not significant predictors of response.
- Time to therapeutic current may influence clinical outcomes, whereas stimulation parameters alone do not predict response.

Statistical Analysis

Mean ± standard deviation or median interquartile range (IQR) and range were used for continuous variables as appropriate. Skewed variables were summarized as median and IQR. Frequencies to present categorical variables as Fisher's exact test, and the Mann-Whitney U test. The effect size was reported using the rank-biserial correlation ($r_{(rb)}$), and a p-value <0.05 was considered significant.

Ethical Approval

Ethical approval was obtained from the ethical committee in Ministry of Health Medical City Welfare Teaching Hospital (approval no: 35, date: 21st November, 2024). All data were anonymized prior to analysis.

RESULTS

The mean age of the total 36 patients was 7.12±3.63 years, and they showed slight male predominance. The mean age at implantation was 6.89±3.62 years, and 14 out of 36 patients had a genetic etiology, as shown in Table 1.

Table 1. Baseline demographic and clinical characteristics of children with VNS implantation

Variables (n=36)	Value
Age (years)	Mean ± SD: 7.12±3.63 Range: 1.3-15
Age at onset (years)	Mean ± SD: 1.86±2.25 Range: 0.3-10
Age at VNS implantation (years)	Mean ± SD: 6.89±3.62 Range :1.3-15
Duration before VNS implantation (years)	Mean ± SD: 5.03±2.73 Range: 0.7-10
Sex	Male: 20/36 Female: 16/36
Baseline seizure frequency (per month)	Median: 80 (60-197) Range: 2-1600
Etiology	Geneti: 15/36 Structural: 14/36 Mixed: 1/36 Unknown: 6/36

VNS: Vagus nerve stimulation, SD: Standard deviation

Responses to VNS therapy varied across etiological groups but did not differ significantly at any evaluated time point (Table 2).

Patients were stratified according the epilepsy onset age (<2 years vs ≥2 years), age of implantation, and era of epilepsy before implantation. There was no statistically significant association between epilepsy onset, age of implantation, and epilepsy duration before VNS implantation and the response to VNS therapy across all time points. Although patients with delayed onset (≥2 years), early implantation (<5 years) had shown slightly higher response at follow-up, yet these findings are based on small subgroup sizes and is not statistically reliable, as shown in Table 3.

Table 2. Response to VNS according to epilepsy etiology at different follow-up intervals

Etiology	Reached therapeutic current of 1.5 mA (n=31)	1 year (n=24)	>1 year (n=18)
Genetic	11/14 95% CI: 52.4-92.4	9/13 95% CI: 42.4-87.3	6/7 95% CI: 48.7-97.4
Structural	7/13 95% CI: 29.1-76.8	7/9 95% CI: 45.3-93.7	7/7 95% CI: 64.6-100
Mixed	0/1 95% CI: 0-79.3	1/1 95% CI: 20.7-100	0/1 95% CI: 0-79.3
Unknown	3/3 95% CI: 43.9-100	1/1 95% CI: 20.7-100	3/3 95% CI: 43.9-100
p-value	**0.27**	**0.58**	**0.33**

Values are presented as number of responders/total (%), with 95% CIs calculated using the Wilson method. Comparisons across etiological groups are performed using Fisher's exact test. CI: Confidence interval, VNS: Vagus nerve stimulation

At 1 year follow-up there was no significant differences in response with different VNS parameter modification (time to first duty cycle adjustment, therapeutic current, current at 1 year, or duty cycle at 1 year), yet non-responders reached therapeutic stimulation slightly later than responders (median 3.5 vs. 3.0 months), as in Table 4.

DISCUSSION

This study evaluates VNS outcomes in Iraqi children with DRE, adding regional evidence to the existing literature. Thirty-one patients were included in this study. These patients were not implanted during a single recruitment time; therefore, follow-up duration varied among participants ,and analyses were done using all patients available at each predefined follow-up interval.

An outpatient's current of 1.5 mA was used as operational cutoff for descriptive analysis. Tamura et al.[14] described the standard therapeutic output current range as 1.5 to 2.25 mA, output current was steadily increased to 1.5 mA followed by further tuning of duty cycle and output current giving the child tolerance and response, therefore in this study 1.5 mA was interpreted as achieving commonly used maintenance level stimulation.

The onset of epilepsy mean was 1.86±2.25 years (range 0.3-10 years) similar to Geng et al.[16] study in China 2023 which included 32 patients who with developmental and epileptic encephalopathy, the study showed a mean age of 22.37±24.70 months (~1.86 years). While another Chinese study by Xie et al.[17] that assessed the effectiveness of VNS in pediatric patients with DRE reported a median onset at 5.5 months emphasizing the early-onset DRE in many pediatric VNS applicants.

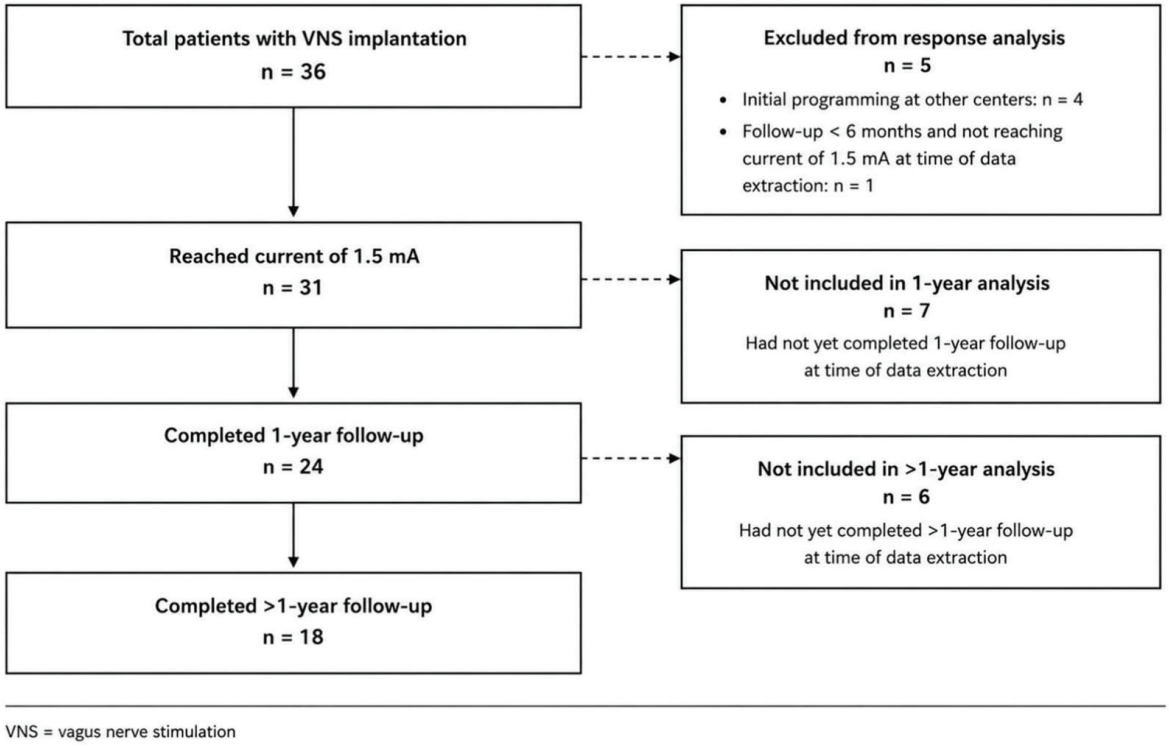


Figure 1. Flow diagram of patients enrolled in the study
VNS: Vagus nerve stimulation

Table 3. Response to VNS according to onset of epilepsy, age of implantation, and duration before implantation at different follow-up intervals

Age of onset of epilepsy	Reached therapeutic current of 1.5 mA	1 year	>1 year	p-value (therapeutic)	p-value (1 year)	p-value (>1 year)
<2 years	14/21	12/17	11/14	**0.72**	**0.41**	**0.52**
≥2 years	8/10	7/7	4/4	**0.72**	**0.41**	**0.52**
Total	**22/31**	**19/24**	**15/18**	—	—	—
Age of implantation of VNS						
<5 years	5/8	6/7	6/7	0.48	0.64	0.64
≥5 years	17/23	13/17	9/11	0.48	0.64	0.64
Total	**22/31**	**19/24**	**15/18**	—	—	—
Duration before VNS implantation						
<2 years	4/6	4/5	4/5	0.71	0.67	0.67
≥2 years	18/25	15/19	11/13	0.71	0.67	0.67
Total	**22/31**	**19/24**	**15/18**	—	—	—

Data are presented as responders/total (percentage). VNS: Vagus nerve stimulation

Table 4. Comparison of current intensity and duty cycle adjustments between responders and non-responders to VNS at 1 year follow-up

Variable	Responders (n=19)	Non-responders (n=5)	p-value	Effect size [$r_{(rb)}$]	Adjusted or (95% CI)	p-value
Time to reach 1.5 mA current (months)	3.0 (2.5-3.5; 2.0-4.0)	3.5 (3.0-4.0; 2.5-12.0)	0.029	-0.20	—	—
Time to first duty cycle change (days)	112 (95.5-233; 0-531)	127 (71-190; 57-218)	0.888	+0.11	1.005 (0.99-1.02)	0.40
Current at 1 year (mA)	3000 (2750-3375; 2000-3500)	3500 (3000-3500; 3000-3750)	0.938	-0.30	0.998 (0.994-1.002)	0.25
Duty cycle at 1 year (%)	38 (35-52.5; 25-57)	49 (49-49; 44-58)	0.272	-0.31	0.93 (0.82-1.05)	0.26

Data are presented as median (IQR; range).Adjusted odds ratios with 95% confidence interval (CI) were derived from multivariate logistic regression. Variables not included in the model are indicated by (—). IQR: Interquartile range,

The duration of epilepsy prior to implantation [mean duration of 5.03±2.73 years (range 0.7-10 yrs)] and the age of implantation (mean age was 6.89±3.62 yrs) was found to be comparable to Xie et al.[17] who reported a median seizure course of 40 months (~3.3 years) and median age at implantation of 4.5 years, while in Geng et al.,[16] mean age of implantation was 4.78±2.76 yrs. However, a study conducted in Iraq to assess patients with VNS implantation at 2015 showed much longer duration before implantation (15.674+/-9.513) years which reflect the change of local practice in epilepsy field across the past 10 years.[18]

Overall, sex distribution seems to vary across studies, but often shows near-equal representation or a slight predominance of one sex. In this cohort, 55.6% were male (20 males, 16 females), indicating a slight male predominance. Hallböök et al.[19] found a male predominance (10 boys, 5 girls), while Geng et al.[16] observed a slight female predominance (17 females, 15 males).

Our patients showed a high baseline seizure frequency range (2-1600/month). Reflecting severe disease burden and surpassing that reported by Chen et al.[20] [30 (6-112.5) per month]. This likely reflects greater severity and differences in reporting.

Regarding epilepsy etiologies, the current cohort exhibited a nearly equal distribution between genetic and structural etiologies (41.6% and 38.9%, respectively). Genetic etiologies were identified in patients with tuberous sclerosis, in a patient with peroxisome biogenesis disorder (*PEX6*), and in a patient with spastic ataxia 5 (*AFG3L2*). Structural defects identified were post-infectious/post-ischemic lesions, hemimegalencephaly, periventricular leukomalacia, post-hypoxic-ischemic encephalopathy, polymicrogyria, and hemispheric atrophy. This is comparable with previous studies like Alwazna et al.[21] identified structural defects in 37.9% of her 103 (pediatric and adult) cohort, while genetic etiologies were found comparably in studies like LoPresti et al.[22] (36%), Grasl et al.[23] (15.1%), and Tamura et al.[14] (26.7%).

Regarding the etiology of epilepsy, the response at any evaluated time point is not statistically significant. Su et al.[24] and Alwazna et al.[21] reported that although VNS response varied across etiologies, it did not consistently predict VNS outcomes in multivariate analysis. These consistent results across different studies may indicate that the mechanism of VNS is network-based rather than lesion-specific.

Both the onset of epilepsy and its duration showed statistically insignificance between VNS responders and non-responders across various follow-up times, as that reported by Geng et al.[16] This is inconsistent with a common hypothesis that intervening earlier in the disease course might yield better results due to less established epileptic networks. Kavčič[25] and Soleman et al.[26] were aligned with this theory. While other researchers reported results that completely contradicted that theory (Grasl et al.[23] and Guo et al.[27]). This could be explained by the heterogeneity of patients' etiologies and types of epilepsy, the complex interactions among individual patient characteristics, VNS programming parameters, and other concurrent treatments. Focusing on isolated demographic factors may not capture the full picture.

The typical practice in VNS programming involves a gradual titration of current from an initial low setting (0.25 mA) to therapeutic levels (typically 1.25-2.0 mA or higher).[28] These procedures take a few months based on patient tolerability and clinical response. While the importance of reaching an effective current is well-established, the speed at which this therapeutic current is achieved has not been clearly reported in the literature to be a consistent prognostic factor.

In this study, the time to first change in duty cycle was shorter in responders than in non-responders, but the difference was not statistically significant. The only statistically significant difference between responders and non-responders was that non-responders required a slightly longer time to reach therapeutic current. However, the small effect size suggests that this finding has limited clinical significance.

No association was observed between stimulation parameters and the response (output current or duty cycle). Notably, non-responders tended to have greater stimulation sets at 1 year, which likely reflects attempts to optimize therapy in patients uncontrolled seizure. These findings support the idea that VNS effectiveness is not solely determined by setting parameters, but rather by patient individualities. In Tzadok et al.[29] cohort titration speed and the onset of clinical response were related, Hachem et al.,[30] suggested that higher stimulation settings can improve seizure control, while D'Andrea-Meira et al.[31] reported that seizure control is achieved through individualized titration, with progressive improvement over time.

A study by Baykan et al.[32] found that reaching an optimal VNS setting (therapeutic current, 10-16% duty cycle) is associated with better response, but aggressive increases beyond that do not improve outcomes. Fahoum et al.[33] found that 1-year response is linked to an adequate VNS dose, rather than slow/low titration, but too extreme escalation beyond the optimal range provides no additional benefit.

Study Limitations

The limitations of this study include a small sample size, especially at later follow-up time points, limiting statistical power. The study was retrospective in a single center without a control group therefore the observed reduction of seizure frequency cannot be certainly attributed to VNS effect alone as concurrent adjustments in anti-seizure medications may have contributed to seizure outcomes. Adjustments to these medications could not be consistently recorded at each time point. The seizure frequency was dependent on parents' reports which may introduce recall bias, also because reaching 1.5 mA was part of the inclusion criteria. The study cannot evaluate outcomes in those who failed to reach this current. Finally, the response was assessed as a reduction in seizure frequency without stratifying by seizure type or epilepsy syndrome, which may influence the assessment of therapeutic response.

Conclusion

VNS therapy was associated with seizure frequency reduction in some children with DRE. The shorter time to reach the therapeutic current was the only aspect of titration dynamics that associated with better clinical benefit. However, because of the small sample size and limited statistical power, these findings should be interpreted carefully.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the ethical committee in Ministry of Health Medical City Welfare Teaching Hospital (approval no: 35, date: 21st November, 2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.A.I., N.W.S., O.A.T., Concept: B.A.I., Design: N.W.S., Data Collection or Processing: B.A.I., N.W.S., O.A.T., Analysis or Interpretation: B.A.I., N.W.S., Literature Search: O.A.T., Writing: B.A.I., N.W.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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