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ORIGINAL PAPER

CLINICAL EFFECTIVENESS OF VAGUS NERVE STIMULATION IN PEDIATRIC DRUG-RESISTANT EPILEPSY: ETIOLOGY-BASED COMPARISON OF GENETIC AND NON-GENETIC COHORTS FOR SEIZURE REDUCTION AND ANTISEIZURE MEDICATION BURDEN

OCENA SKUTECZNOŚCI STYMULACJI NERWU BŁĘDNEGO W LECZENIU PEDIATRYCZNEJ PADACZKI LEKOOPORNEJ: ANALIZA PORÓWNAWCZA KOHORT O PODŁOŻU GENETYCZNYM I NIEGENETYCZNYM W ZAKRESIE KONTROLI NAPADÓW I REDUKCJI OBCIĄŻENIA FARMAKOTERAPIĄ PRZECIWPADACZKOWĄ

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SUMMARY

Introduction

Drug-resistant epilepsy (DRE) affects up to 40% of pediatric patients and continues to be a major therapeutic challenge. Vagus nerve stimulation (VNS) is an established neuromodulatory therapy; however, the impact of genetic etiology on treatment efficacy and antiseizure medication (ASM) burden remains unclear.

Aim

To evaluate the clinical effectiveness of VNS in pediatric DRE, comparing seizure reduction and ASM burden between genetically and non-genetically determined epilepsies.

Materials and methods

We retrospectively analyzed 18 pediatric patients (aged 4–18 years) with DRE who underwent VNS implantation between 2021 and 2025. Patients were stratified into genetic (n = 8) and non-genetic (n = 10) cohorts. Seizure frequency and ASM exposure were in comparison to before and after implantation using nonparametric tests. The significance level was set at $p < 0.05$. Median duration of VNS therapy was 15 months (interquartile range [IQR] width: 16 months).

Results

Overall, 67% of individuals exhibited clinical improvement, and 61% achieved a ≥ 50% reduction in seizure frequency. Median seizure reduction appeared greater in the non-genetic cohort (60%) than in the genetic cohort (20%), although this difference did not reach statistical significance (p = 0.088). Reduction in ASM burden occurred in 50% of non-genetic cases versus 13% of genetic cases. Post-implantation exposure to calcium-channel modulators was significantly more frequent amongst non-genetic patients (p = 0.036).

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Conclusions
VNS provides clinically observable seizure reduction in pediatric DRE regardless of etiology, though responses appear more pronounced in non-genetic cases. Genetic etiology should not preclude VNS consideration, as it remains a safe and effective adjunctive therapy for refractory epilepsy.

Keywords: VNS, neuromodulation, pediatric drug-resistant epilepsy, epilepsy

STRESZCZENIE
Wstęp
Padaczka lekooporna (DRE) dotyczy nawet 40% pacjentów pediatrycznych i nadal stanowi istotne wyzwanie terapeutyczne. Stymulacja nerwu błędnego (VNS) jest uznaną metodą neuromodulacji, jednak wpływ etiologii genetycznej na skuteczność leczenia oraz obciążenie farmakoterapią przeciwpadaczkową (ASM) pozostaje nie w pełni wyjaśniony.
Cel
Ocena skuteczności klinicznej VNS w pediatrycznej DRE poprzez porównanie redukcji częstości napadów oraz zmian w zakresie stosowania ASM pomiędzy padaczkami o podłożu genetycznym i niegenetycznym.
Materiały i metody
Retrospektywnie przeanalizowano 18 pacjentów pediatrycznych (w wieku 4–18 lat) z DRE, u których w latach 2021–2025 wszczepiono układ VNS. Chorych podzielono na kohortę o etiologii genetycznej (n = 8) oraz niegenetycznej (n = 10). Częstość napadów i ekspozycję na ASM porównano przed i po implantacji z wykorzystaniem testów nieparametrycznych. Za poziom istotności statystycznej przyjęto $p < 0.05$. Mediana czasu terapii VNS wyniosła 15 miesięcy [szerokość przedziału międzykwartylowego (IQR width): 16 miesięcy].
Wyniki
Kliniczną poprawę uzyskano u 67% pacjentów, a 61% osiągnęło redukcję częstości napadów ≥ 50%. Mediana redukcji napadów była większa w kohorcie niegenetycznej (60%) niż genetycznej (20%), jednak różnica ta nie osiągnęła istotności statystycznej (p = 0.088). Zmniejszenie obciążenia ASM stwierdzono u 50% chorych z grupy niegenetycznej oraz u 13% z grupy genetycznej. Po implantacji istotnie częściej stosowano modulatory kanałów wapniowych u pacjentów z padaczką o etiologii niegenetycznej (p = 0.036).
Wnioski
Stymulacja nerwu błędnego zapewnia klinicznie istotną redukcję napadów u dzieci z DRE niezależnie od etiologii, choć odpowiedź na leczenie wydaje się bardziej wyraźna w przypadkach o podłożu niegenetycznym. Etiologia genetyczna nie powinna wykluczać kwalifikacji do VNS, która pozostaje bezpieczną i skuteczną metodą leczenia wspomagającego u pacjentów z padaczką lekooporną.

Słowa kluczowe: VNS, neuromodulacja, pediatryczna padaczka lekooporna, padaczka

Introduction
Epilepsy is amongst the most common neurological disorders, affecting approximately 1% of the population, corresponding to about 50 million individuals worldwide [1,2]. Antiseizure medications (ASMs) remain the first-line therapy, however, approximately 30–40% of newly diagnosed patients exhibit inadequate response to initial treatment, and only about half achieve a 50%

reduction in seizure burden. Drug-resistant epilepsy (DRE) is defined when adequate trials of two appropriately selected and well-tolerated ASM regimens, whether administered separately as monotherapies or in combination as polytherapy, fail to produce sustained seizure reduction [2,3]. DRE poses significant challenges being frequently associated with comorbidities, higher mortality, cognitive impairment, and reduced quality of life, necessitating alternative therapeutic approaches [4]. In generalized DRE, treatment options are limited and include ASMs, neuromodulation including vagus nerve stimulation (VNS), or palliative surgery such as lesionectomy and corpus callosotomy. Resective surgery remains the treatment of choice for suitable candidates with a localized and resectable focus, although fewer than 40% of patients meet these criteria [3]. VNS should be considered as a second-line option for patients who are not candidates for resective surgery due to the multifocal or non-lesional epilepsy. Seizure outcomes after VNS are generally inferior to those following resective epilepsy surgery [5]. Patients suitable for resection should thus be prioritized for surgical evaluation before VNS is considered.

VNS exhibits a time-dependent antiseizure effect, although the precise mechanisms underlying its acute and chronic efficacy remain incompletely elucidated [6,7]. It is hypothesised that VNS induces neural desynchronization through afferent vagal pathways, leading to suppression of interictal epileptiform activity in responsive individuals, thereby exerting a broader neuromodulatory effect on cortical and subcortical networks [8,9,10]. Emerging evidence suggests enhancement of cerebral perfusion and increased synaptic activity within multiple central nervous system structures, including the locus coeruleus, the dorsal raphe nucleus, and regions of the thalamus, hypothalamus, neocortex, and cerebellum [11,12]. In this context, VNS might reduce seizure duration, attenuate ictal and postictal severity, limit seizure clustering, and decrease seizure-related hospitalizations.

In children, epilepsy arises from diverse causes, however, genetic etiologies are increasingly recognized. An expanding body of evidence indicates that genetic factors play a significant role in the pathogenesis and development of epilepsy [8,9]. Underlying genetic etiology may consist of single-gene mutations associated with channelopathies or synaptic dysfunction, chromosomal abnormalities, and microdeletions, among others. At least 500 epilepsy-associated genes have been detected since 1995, although many remain insufficiently characterized and of uncertain significance. Despite advances in sequencing, more than half of children suspected of having epilepsy of genetic etiology do not have access to appropriate diagnostics and remain undiagnosed. Idiopathic generalized epilepsies, also termed genetic generalized epilepsies, account for approximately 15–20% of all cases and comprise childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone [11]. Although VNS is a viable option in well-characterized genetic epileptic encephalopathies, including Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex, its effectiveness in pediatric DRE with other rare gene mutations remains uncertain [13]. The literature specific to seizure outcomes after VNS in pediatric genetically determined DRE is scarce, with relatively few case–control studies and cohort analyses. Currently, a patient's genetic etiology is not considered in routine presurgical assessment of adult patients with epilepsy, as its influence on surgical outcomes is poorly understood [14]. A recent prospective cohort reported that surgical intervention, including neurostimulation, controlled seizures in children with genetically refractory epilepsy, even in magnetic resonance imaging-negative cases [15]. Although the impact of VNS on seizure reduction across

various etiologies has been examined, a gap persists regarding the role of genetic etiology and its implications for reducing ASM burden and seizure frequency.

Neuromodulation techniques are a viable therapeutic option for individuals with genetic epilepsy who are not eligible for resective or disconnective procedures [16]. Earlier consideration and implantation of VNS may improve treatment responsiveness and reduce pharmacoresistance progression, particularly in epileptic encephalopathies with early seizure onset. Many genetically determined seizures begin in early infancy, which is a crucial neurodevelopment period. Therefore, effective therapeutic intervention should be considered early in the course of the disease [17].

Aim

The aim of this study was to compare the clinical effectiveness of VNS in patients with DRE of genetic versus other etiologies. The primary objective was to evaluate seizure reduction after VNS, expressed as relative percentage change and the proportion achieving a ≥ 50% response. Secondary objectives include changes in ASM burden and exposure by mechanistic class before and after VNS, with comparisons across etiological strata.

Materials and methods

Participants and study design

This is a retrospective, observational cohort study conducted at the Department of Children Neurosurgery, Children's University Hospital in Krakow, Poland. Clinical data were extracted from institutional electronic medical records spanning years 2021–2025. The study cohort included eighteen pediatric patients (aged 4 –18 years; both sexes) who underwent VNS implantation for DRE. Inclusion criteria were: (1) age < 18 years at implantation, (2) documented diagnosis of DRE according to International League Against Epilepsy criteria, defined as a failure of two appropriately selected ASM, (3) and availability of complete medical records covering the periods before and after VNS implantation. Exclusion criteria included: (1) patients aged ≥ 18 years at implantation; (2) missing pre- or post-implantation clinical documentation; or (3) insufficient follow-up over 12 months.

Data collection

Data extraction was performed by qualified clinicians. Acquired variables included patient demographics, seizure type, etiology of epilepsy, the number and types of ASMs taken before and after VNS implantation, the number of seizures before and after VNS implantation, age at VNS implantation, length of follow-up, and time to stimulator activation. Seizure frequency was derived from caregiver-reported seizure diaries and outpatient clinic documentation. Baseline seizure frequency was calculated as the mean monthly seizure count during the 3 months preceding VNS implantation. Genetic etiology was defined as epilepsy with confirmed pathogenic or likely pathogenic variant detected by next-generation sequencing or chromosomal microarray analysis. Variants of uncertain significance were excluded. In cases of uncertain or inconsistent reports, data were cross-checked with available clinical records.

Study outcomes

The primary outcome of the study was the clinical efficacy of VNS, defined as the median percentage reduction in seizure frequency following device implantation compared with the pre-implantation baseline. Efficacy was quantified as the median change in seizure frequency and as the proportion of patients achieving a ≥ 50% reduction in seizure frequency. Clinical improvement was defined as any reduction in seizure frequency observed after VNS implantation compared with the pre-implantation baseline period. To ensure objective and comparable

assessment of therapeutic effectiveness, we applied the McHugh classification, one of the most widely used outcome measures in studies of VNS. This five-grade scale provides a standardized framework for quantifying seizure reduction, with Classes I–II denoting clinically meaningful improvement (≥ 50% reduction). Its use is particularly valuable in heterogeneous pediatric cohorts, as it enables consistent reporting of treatment outcomes regardless of underlying etiology, seizure phenotype, or follow-up duration. Class I indicates > 90% seizure reduction, reflecting an excellent therapeutic response. Class II corresponds to a 75–90% reduction, representing substantial improvement. Class III denotes a 50–75% reduction and is considered the threshold for clinically meaningful response. Class IV captures < 50% seizure reduction, indicating partial or limited benefit. Class V reflects absence of improvement or seizure worsening.

Secondary outcomes included (1) change in ASM burden, expressed as the difference in the number of total concomitant ASM before and after VNS implantation, (2) change in exposure to specific mechanistic classes of ASMs [sodium-channel modulators, calcium-channel modulators, GABAergic agents, synaptic vesicle glycoprotein 2A (SV2A) inhibitors, and mixed/other mechanisms].

Statistical analysis

Normality of distribution of variables was assessed using the Shapiro-Wilk test. As most variables deviated from normality, continuous variables are reported as medians with interquartile range (IQR) width. IQR width was calculated as the difference between the third and first quartiles (Q3–Q1) and is presented as a single numerical value. Given predominance of non-normally distributions, between-group comparisons of continuous variables were performed using the Mann-Whitney *U* test, and categorical variables were compared using the one-tailed Fisher's exact test. The significance of the difference between two-stage distributions was assessed by the one-tailed Fisher's exact test. Within-group comparisons were assessed using the McNemar's test and the sign test. Statistical significance was set at $p < 0.05$. Statistica 10 PL package was used for the analysis.

Ethics approval and data protection

This study was conducted in accordance with institutional, national, and international ethical standards, including the Declaration of Helsinki and relevant data protection regulations. Ethical approval was waived, as the study involved a retrospective analysis of fully anonymized clinical and imaging data obtained during routine medical care, with no impact on diagnostic or therapeutic procedures. All patients and/or their legal guardians were informed during the course of treatment about the potential use of anonymized clinical data for scientific and educational purposes. Patient confidentiality was safeguarded throughout the study. All data were anonymized prior to analysis, and no identifiable personal information was used or stored. Data access was restricted to authorized members of the research team.

Results

Demographics and clinical characteristics

A total of eighteen pediatric patients with DRE who underwent VNS implantation between 2021 and 2025 fulfilled inclusion criteria. Eight children presented with genetic etiology, and ten had epilepsy of other origins (e.g., structural or unknown causes). Within the genetic etiology subgroup, phenotypes comprised four monogenic epilepsies, two cases of West syndrome, and single cases of Lennox-Gastaut and Dravet syndromes. The overall median age at implantation was 107.5 months (IQR width: 97.0). In the genetic group, the VNS was implanted at 102.0 months (IQR width: 102.5), and in the non-genetic group it was 113.0 months (IQR width: 87.0), with no between-group difference

(p = 0.96). The proportion of male patients was higher in the genetic group (62.5% vs. 40%), although this difference did not reach statistical significance. Anthropometric parameters of weight and height, both absolute and percentile-adjusted, did not significantly differ between groups. Seizure semiology, including focal, generalized, and secondarily generalized seizures, was evenly distributed. Structural or focal lesions were more frequent in the non-genetic group, occurring in 80% of patients compared with 50% of patients with genetic etiology, although this difference did not reach statistical significance (p = 0.20) (Table 1).

The median age at epilepsy onset was earlier in the genetic group (6.0 vs. 10.5 months; p = 0.68), yet without statistical significance. Duration of epilepsy prior to VNS implantation was similar across cohorts (genetic: 89.0 months; non-genetic: 92.5 months; p = 0.60). The median duration of VNS therapy at the time of evaluation was 15.0 months (IQR width: 16.0) across the entire cohort, with no significant difference between groups. The stimulator was activated a median of 29.0 days (IQR: 11.0) post-implantation in both groups, aligning with standard clinical practice (Table 1). In genetic epilepsies, regression models did not achieve convergence due to sample size limitations, yet the descriptive trend suggested reduced response rates. These findings imply that patient-related factors such as age, sex, or body weight exert limited influence on VNS efficacy, and that treatment response may primarily depend on the underlying neurobiological substrate.

Primary outcomes: seizure frequency reduction after VNS implantation

Clinical response to VNS, assessed by change in seizure frequency, varied between groups. Overall, 61% of patients achieved a clinically

Table 1. Baseline demographic and clinical characteristics of the study cohort, stratified by etiology of epilepsy (genetic vs. non-genetic). Continuous variables are presented as median (IQR width). IQR width was calculated as Q3–Q1 and reported as a single numerical value. Categorical variables are presented as *n* (%). *P*-values were calculated using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables

Variable	Epilepsy of genetic etiology (n = 8)	Epilepsy of non- genetic etiology (n = 10)	p-value	All patients (N = 18)
Sex (male)	5 (62.5%)	4 (40)	0.31	9 (50)
Age (months)	110.5 (103.5)	121.0 (79.0)	0.76	110.5 (92.0)
Body mass (kg)	24.0 (22.10)	44.0 (25.0)	0.74	28.0 (27.5)
Body mass percentile	20.0 (42.0)	43.0 (57.0)	0.47	21.0 (57.0)
Height (cm)	134.0 (44.0)	150.0 (31.0)	0.60	143.0 (38.0)
Height percentile	29.0 (56.0)	29.5 (55.0)	0.64	29.0 (55.0)
Focal seizures	4 (50)	6 (60)	0.52	10 (56)
Secondary generalized seizures	2 (25)	4 (40)	0.44	6 (33)
Generalized seizures	6 (75)	7 (70)	0.62	13 (72)
Psychogenic seizures	0 (0)	1 (10)	0.56	1 (6)
Age at seizure onset (months)	6.0 (23.0)	10.5 (35.5)	0.68	10.0 (21.0)
Epilepsy duration (months)	89.0 (85.0)	92.5 (59.5)	0.60	92.0 (71.0)
Genetic etiology	8 (100)	0 (0)	< 0.0001	8 (44)
Focal lesion/structural etiology	4 (50)	8 (80)	0.20	12 (67)
Age at VNS implantation (months)	102.0 (102.5)	113.0 (87.0)	0.96	107.5 (97.0)
Duration of VNS therapy (months)	12.5 (19.5)	15.0 (13.0)	0.42	15.0 (16.0)
Time to stimulator activation after implantation (days)	29.0 (18.0)	33.5 (12.0)	0.47	29.0 (11.0)

VNS – vagus nerve stimulation

meaningful response defined as ≥ 50% seizure reduction, with a median seizure reduction of 55% (IQR: 70) across the entire cohort. Individual responses were heterogeneous, ranging from minimal change to near-complete seizure control (Figure 1). Although these differences were not statistically significant (p = 0.0882), the trend indicates greater efficacy of VNS in non-genetic DRE (Table 2).

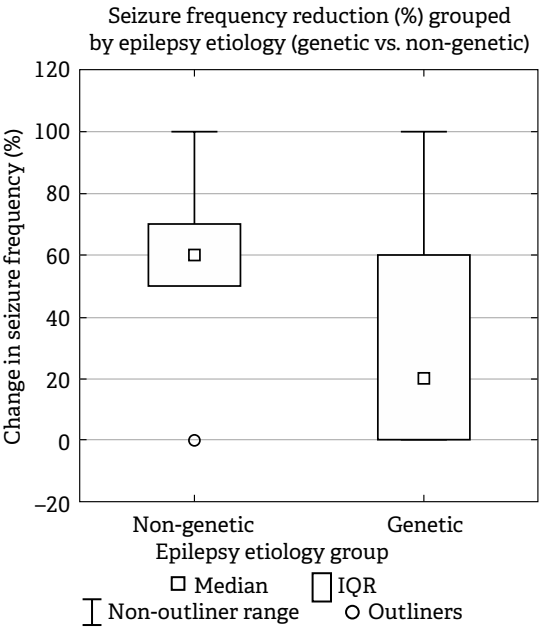

Figure 1. Seizure frequency reduction according to epilepsy etiology. Boxes represent the interquartile range, horizontal lines indicate the median, whiskers denote the non-outlier range, and circles mark outliers

Secondary outcomes: changes in ASM burden

Across the entire cohort, the median number of ASMs before and after implantation remained stable at 3.0 (1.0). One third of all patients experienced a reduction in the number of concomitant ASMs after implantation. In the genetic group, a reduction in ASM burden was observed in only one patient (13%), whereas five patients (50%) in the non-genetic group demonstrated a decrease (p = 0.0882). These findings suggest a more favorable impact of VNS on ASM load in children with non-genetic epilepsy. Post-implantation exposure to most mechanistic classes remained largely stable between groups. The most significant observed difference was the markedly greater use of calcium-channel modulators in the non-genetic group, where 60% received this class compared with 13% in the genetic group; this difference was statistically significant (p = 0.036). Use of other classes after implantation did not differ materially between groups (Table 3). Changes in ASM burden and mechanistic exposure reflect real-world post-implantation clinical management and should not be interpreted as direct pharmacodynamic effects of VNS.

Pre–post VNS changes in mechanistic ASM exposure

Changes in ASM exposure by mechanistic class were also examined. Before implantation, ion-channel modulators were the most frequently used in both groups. Following VNS, use of calcium-channel modulators significantly decreased in the genetic group (from 25% to 13%; p = 0.0412), while exposure remained unchanged in the non-genetic group

Table 2. Clinical outcomes after vagus nerve stimulation according to epilepsy etiology. The table summarizes post-implantation effectiveness and treatment burden at the last available visit, including any clinical improvement, percentage change in seizure frequency and the ≥ 50% responder proportion. Data are shown as *n* (%). *P*-values were calculated using Fisher's exact test

Variable	Epilepsy of genetic etiology (*n* = 8)	Epilepsy of non- genetic etiology (*n* = 10)	*p*-value	All patients (*N* = 18)
Post-implantation clinical improvement	4 (50)	8 (80)	0.20	12 (67)
Percentage change in seizure frequency	20.0 (60.0)	60.0 (20.0)	0.20	55.0 (70.0)
≥ 50% reduction in seizure frequency	3 (38)	8 (80)	0.0882	11 (61)

Table 3. Antiseizure medication (ASM) burden and mechanistic class exposure before and after vagus nerve stimulation implantation. The number of concomitant ASMs is presented as median with interquartile range (IQR) width calculated as Q3–Q1 and reported as a single numerical value. ASM class exposure is presented as *n* (%). *P*-values were calculated using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables

Variable	Epilepsy of genetic etiology (*n* = 8)	Epilepsy of non-genetic etiology (*n* = 10)	*p*-value	All patients (*N* = 18)
Reduction in number of concomitant ASMs	1 (13)	5 (50)	0.0882	6 (33)
Number of concomitant ASMs before implantation	3.0 (1.0)	3.0 (1.0)	0.35	3.0 (1.5)
Type of ASM before implantation				
Ion channel modulator, any	7 (88)	8 (80)	0.59	15 (83)
Sodium channel modulator	7 (88)	6 (60)	0.23	13 (72)
Calcium channel modulator	2 (25)	3 (30)	0.62	5 (28)
GABAergic agents	2 (25)	3 (30)	0.57	5 (28)
Diverse mechanism	5 (68)	5 (50)	0.48	10 (56)
SV2A inhibitors	3 (37.5)	4 (40)	0.60	7 (39)
Non-ASM agents	2 (25)	4 (40)	0.44	6 (33)
Number of concomitant ASMs after implantation	3.0 (1.0)	3.0 (1.0)	0.81	3.0 (1.0)
Type of ASM after implantation				
Ion channel modulator, any	7 (88)	9 (90)	0.47	16 (89)
Sodium channel modulator	7 (88)	7 (70)	0.55	14 (78)
Calcium channel modulator	1 (13)	6 (60)	0.0364	7 (39)
GABAergic agents	4 (50)	4 (40)	0.60	8 (56)
Diverse mechanism	5 (63)	7 (70)	0.44	12 (67)
SV2A inhibitors	3 (38)	4 (40)	0.58	7 (39)
Non-ASM agents	2 (25)	1 (10)	0.41	3 (17)

SV2A – synaptic vesicle glycoprotein 2A

Table 4. Within-group pre–post comparisons of antiseizure medication (ASM) use and counts. *P*-values refer to paired comparisons between pre- and post-vagus nerve stimulation (VNS) assessments within each etiological subgroup and in the overall cohort. McNemar's test was applied to binary exposure variables (by ASM class), and the sign test to paired counts of ASMs. Non-ASM agents refer to medications not primarily indicated for seizure control

Variable	Epilepsy of genetic etiology *p*-values (pre- vs. post-VNS) (*n* = 8)	Epilepsy of non-genetic etiology *p*-values (pre- vs. post-VNS) (*n* = 10)	Overall cohort *p*-values (pre- vs. post-VNS) (*N* = 18)
Number of concomitant ASMs	0.48	0.61	0.68
Type of ASM			
Ion channel modulator, any	0.13	1.0	0.0020
Sodium channel modulator	0.13	0.45	0.0614
Calcium channel modulator	0.0412	1.0	0.23
GABAergic agents	0.68	0.37	0.23
Diverse mechanism	1.0	0.68	0.58
SV2A inhibitors	0.62	0.68	0.75
Non-ASM agents	0.44	0.62	0.23

SV2A – synaptic vesicle glycoprotein 2A

(60% pre- and post-implantation). In the cohort as a whole, exposure to ion-channel modulators increased ($p = 0.0020$). A borderline shift was observed for sodium-channel modulators ($p = 0.0614$). For GABAergic agents, mechanistically diverse agents, SV2A inhibitors and non-ASM agents, no significant within-group changes were detected (Table 4).

Discussion

The present study evaluated the clinical effectiveness of VNS in a pediatric cohort with DRE, comparing outcomes between patients with genetically determined and non-genetic forms of epilepsy. The results demonstrated that VNS led to a clinically meaningful reduction in seizure frequency in the majority of children, with 61% achieving at least a 50% response. While a higher proportion of responders was observed in non-genetic epilepsies (80%) compared with genetically mediated cases (38%), this difference did not reach statistical significance, likely reflecting the limited sample size and underlying genetic heterogeneity. Nevertheless, these findings are consistent with previous reports showing that VNS remains effective across a spectrum of pediatric epilepsies, including those of genetic origin, and that response rates improve progressively over time following implantation.

Efficacy of neuromodulation in pediatric DRE

Cumulative evidence indicates that VNS is an effective and safe neuromodulatory option with heterogeneous but substantial response rates between 25%–66% depending on the population and duration of follow-up [18,19,20]. The present findings align closely with long-term studies where > 50% seizure reduction was achieved in 39%–65% [19,20]. Very few case series to date have examined the outcomes of epilepsy surgery in patients with monogenic epilepsies. Existing literature on neuromodulation in genetic epilepsies suggests an increased risks of poor surgical outcomes [14]. Our cohort's response rate among genetically determined epilepsies 38%, with overall responsiveness of 50%, closely to the pooled response reported in the largest available meta-analysis of VNS in genetic epilepsies by Hajtovic *et al.* [4]. Importantly, although seizure reduction was less pronounced in the genetic group and did not reach statistical significance, the observed changes may still be of clinical relevance at the individual patient level. These findings support the emerging consensus that VNS should not be excluded a priori in patients with genetically determined epilepsies, such as *SCN1A*-related Dravet syndrome, tuberous sclerosis complex, and Rett syndrome.

The influence of underlying genetic etiology on VNS responsiveness is multifactorial. Many epilepsy-associated genes, including *SCN1A*, *GABRA1*, *CHD2*, and *KCNQ2*, encode ion-hannels or synaptic proteins that influence network excitability. VNS is thought to modulate cortical and subcortical synchrony through activation of afferent projections from the nucleus tractus solitarius to the locus coeruleus, thalamus, and limbic circuits. This pathway enhances noradrenergic and serotonergic tone, resulting in desynchronization of hypersynchronous epileptic networks. Functional imaging studies have confirmed increased regional cerebral blood flow and synaptic activity within these circuits after chronic stimulation, supporting the neurobiological plausibility of VNS efficacy across heterogeneous epileptic syndromes [4].

ASM burden and pharmacoresistance

The impact of VNS on ASM burden remains controversial. In our study, the median number of ASMs remained stable at three agents, with only 13% of patients in the genetic group, compared to 50% of those with non-genetic etiologies, reducing their ASM load after implantation. This finding mirrors prior multicenter data where seizure frequency decreased significantly after VNS, but ASM regimens often remained unchanged [21]. Such stability reflects clinical

caution in tapering ASMs in children with severe epilepsy, particularly those with genetic syndromes or history of status epilepticus. These findings reflect clinical observations that VNS is often more effective in lesional or focal epilepsies than in epileptic encephalopathies and monogenic epilepsies. Evidence regarding the impact of VNS on ASM burden remains inconclusive, with some studies reporting stable or increased ASM use despite clinical improvement. De Herdt *et al.* [22] reported that the mean number of ASMs remained unchanged even after many years of VNS stimulation. They found that treatment was increased or additional ASM therapy was added in 76.7% of patients. In the study by Arcand *et al.* [23], 33% of VNS patients had a change in ASM at 12 months, 59% at 24 months, and 81% at 36 months. Currently, there is no high-quality evidence supporting a consistent effect of VNS implantation on the reduction of ASM count. Predictive factors identifying patients who might benefit from dose or drug reduction have not yet been established, and this relationship appears to be highly individualized. Furthermore, the number of prescribed ASMs does not correlate significantly with seizure control after VNS implantation [24]. An increase in the number or dosage of ASMs following VNS should not be regarded as a therapeutic failure if seizure reduction results in cognitive improvement and enhanced quality of life. Potnis *et al.* [25] reported an increase in ASM use in over half of VNS-treated patients, accompanied by meaningful seizure reduction. These findings suggest that, while ASM additions have a low probability of producing seizure freedom, they still contribute to a gradual decrease in seizure burden. The identification of ASMs exerting synergetic effects with VNS is of major importance [26]. Understanding such synergism could facilitate optimization of therapeutic regimens and improvement of patient outcomes. To date, only two studies have investigated combinations of VNS with different ASMs, identifying two potentially favorable interactions [27]. Multiple regression analyses exemplified that combinations of VNS with SV2A modulators or slow sodium-channel inhibitors were associated with significantly higher responder rates and a greater likelihood of seizure freedom than combinations involving ASMs targeting alternative mechanisms of action [26]. In our study, exposure by mechanistic class was largely unchanged, except for two findings. First, cohort-level exposure to ion-channel modulators increased on paired analysis, possibly reflecting routine post-implantation pharmacological optimization strategies rather than any direct pharmacodynamic interaction with VNS. However, our findings warrant confirmation in controlled, blinded studies to establish causality. Second, calcium-channel modulators use decreased within the genetic group but was more frequent post-implantation in the non-genetic cohort. This differential use most likely reflects routine, individualized post-implantation ASM titration rather than a direct pharmacodynamic interaction with VNS, and should therefore be interpreted as an association rather than evidence of synergistic efficacy, given the absence of data supporting calcium-channel antagonism as a synergistic mechanism. However, VNS may indirectly support dose reduction or simplification of ASM regimens by improving seizure control, thereby reducing behavioral adverse effects and enhancing mood through its central nervous system neuromodulatory properties. A deeper understanding of possible synergistic interactions between VNS and ASMs with specific mechanisms of action could optimize therapeutic responses and mitigate treatment-related side effects. As the number of epilepsy patients benefiting from VNS increases, it remains unclear which ASMs work in synergistic manner with this type of neuromodulation [26]. The independent pharmacological impact of VNS on post-implantation therapy remains poorly defined, due to the influence of specific drug

changes and device parameter optimization during long-term follow-up. The independent effects of VNS are inherently difficult to measure in clinical practice. Antiepileptic drugs, VNS output, and lifestyle factors are consistently adjusted to optimize seizure control. It has been suggested that VNS patients may still experience a time-dependent reduction in seizure frequency, even without modifications in ASMs [15,17,24]. Another confound concerns the unknown impact that changes in ASM regimens have on seizure frequency over time in the setting of VNS. Many follow-up visits involved both VNS parameter adjustments and, more frequently, changes to ASM regimens. Although these could not be controlled for in our analysis, we believe that concurrent pharmacotherapy plays a major role in the long-term success of any treatment strategy, including VNS [28].

Clinical translation and future directions

The variability in response to VNS underscores the need for reliable predictors of efficacy. Clinical parameters such as younger age at implantation, shorter epilepsy duration, and focal seizure types have been consistently associated with better outcomes [29]. Early implantation, ideally within the first decade of life, may enhance responsiveness by mitigating maladaptive neuroplasticity and chronic network hyperexcitability. Advanced electrophysiological biomarkers, such as electroencephalography (EEG) desynchronization and entropy measures, also show promise in predicting outcomes [30] A multimodal model combining clinical and EEG synchronization features has been developed to discriminate responders, achieving robust predictive accuracy [30]. Integrating such quantitative markers with genetic profiles could substantially refine patient selection and parameter optimization.

The present findings add to the growing body of evidence supporting VNS as a viable adjunctive therapy in both genetic and non-genetic pediatric DRE. Moving forward, the integration of molecular diagnostics, connectomics, and quantitative neurophysiology offers the potential for precision neuromodulation, tailoring stimulation parameters and timing to individual neurobiological profiles. The robust implementation of genetic testing in the clinical setting may enhance genetic diagnosis and allow further study of etiology-specific therapeutic outcomes. Patients who fail to respond adequately to ASM should be considered for VNS therapy. According to the current guidelines for VNS implantation, genetically determined epilepsies are not a contraindication, thus this intervention may substantially improve seizure control and overall quality of life [29]. By characterizing the therapeutic responses to VNS across diverse genetic etiologies, we can improve access in order to at least palliate seizure burden and to optimize outcomes in affected children who otherwise have no known cure at present [4].

Limitations

This study has several limitations. The small sample size and single-center design limit statistical power and generalizability, restricting the ability to detect subtle intergroup differences. The retrospective, observational design precluded randomization and blinding, introducing potential selection bias, information bias, and residual confounding. Seizure outcomes were primarily based on caregiver-reported seizure frequencies, which are subject to recall and reporting bias and may lead to under- or overestimation of seizure burden. In addition, substantial heterogeneity in genetic variants, epilepsy phenotypes, and VNS parameters may have influenced individual treatment responses and limit etiology-specific inference. Concurrent adjustments of ASM regimens during follow-up represent an important confounding factor, making it difficult to attribute seizure reduction exclusively to neuromodulation. Accordingly, the present findings should be interpreted as descriptive and hypothesis-

generating. Despite these limitations, the study reflects real-world clinical practice and suggests that VNS is a safe and well-tolerated adjunctive treatment option in pediatric DRE. Larger prospective, multicenter studies with genotype-stratified designs and standardized protocols are needed to confirm these observations.

Conclusions

This study suggests that VNS remains an effective and safe adjunctive therapy for pediatric DRE, including cases with confirmed genetic etiology. Although seizure reduction appeared greater in non-genetic epilepsies, children with genetic forms also demonstrate individual-level improvements, with over one-third achieving at least a 50% reduction in seizure frequency. These findings indicate that a genetic diagnosis alone should not preclude consideration of VNS in children with DRE. Importantly, this therapy may still yield substantial benefits in seizure control and quality of life. Predictors of VNS efficacy remain incompletely defined, reflecting heterogeneity in underlying pathophysiology and limited genotype-specific data. Broader implementation of genetic testing in pediatric epilepsy, combined with large-scale, prospective, and long-term genotype-stratified studies, may help elucidate patterns of seizure freedom and treatment responsiveness over time. Integration of molecular and clinical profiling into presurgical evaluation pathways may enable more precise patient selection and optimize long-term outcomes in refractory epilepsy.

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