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SHORT RESEARCH ARTICLE

Fenfluramine in SCN1A-related GEFS+: A multicenter observational study on efficacy, EEG improvement, and tolerability

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Abstract

The *SCN1A* gene is implicated in a broad spectrum of epilepsy phenotypes, ranging from self-limited genetic epilepsy with febrile seizures plus (GEFS+) to severe developmental and epileptic encephalopathies such as Dravet syndrome (DS). While fenfluramine (FFA) has demonstrated strong efficacy in DS, its role in *SCN1A*-related epilepsies beyond DS has not been thoroughly investigated. We conducted a multicenter observational study including 11 patients with *SCN1A*-related GEFS+ who received FFA as adjunctive therapy. All patients had

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previously failed to achieve adequate seizure control with valproate and, in most cases, additional antiseizure medications. FFA was introduced following the DS titration protocol, with a mean dose of 0.39 mg/kg/day. FFA addition led to a mean seizure frequency reduction of 91%, with more than half of the patients achieving complete seizure freedom. Reduced EEG abnormalities were documented in 5/11 patients of the cohort, including complete normalization in 3/11 patients. Furthermore, subjective caregiver reports indicated perceived improvements in patients' alertness and behavioral responses. FFA was well tolerated, with only mild and transient adverse events reported. These findings support the potential role of FFA as an effective and well-tolerated treatment option in patients with *SCN1A*-related GEFS+.

Plain Language Summary: GEFS+ is a genetic epilepsy frequently caused by changes in the SCN1A gene. In a multicenter real-world study of 11 people with SCN1A-related GEFS+, adding fenfluramine to usual care substantially reduced seizures, with several becoming seizure-free. EEG recordings improved, and caregivers reported better alertness in some patients. Treatment was generally well tolerated, with only mild, temporary side effects.

KEYWORDS

Dravet syndrome, fenfluramine, GEFS+, genotype–phenotype correlation, real-world evidence, SCN1A

1 | INTRODUCTION

The *SCN1A* gene encodes the alpha-1 subunit of the voltage-gated sodium channel (Nav1.1) and is implicated in a broad spectrum of epileptic disorders ranging from febrile seizures to self-limited genetic epilepsy with febrile seizures plus (GEFS+) and extends to severe developmental and epileptic encephalopathies, such as Dravet syndrome (DS).[1]

DS typically manifests within the first year of life with prolonged febrile and afebrile generalized clonic or hemiclonic seizures. Between ages 1 and 4 years, additional seizure types, including myoclonic, focal, and atypical absence seizures, often emerge. Seizures are typically pharmacoresistant, prolonged, and tend to occur in clusters, frequently progressing to status epilepticus. Cognitive, behavioral, and motor impairments usually become evident in the second year of life.[2] *SCN1A* pathogenic variants are identified in up to 80% of DS patients.[3]

GEFS+ was first described in 1997 within large families exhibiting dominant inheritance of febrile seizures. Affected patients may experience febrile seizures that occur either before 6 months or after 6 years of age, as well as afebrile generalized or focal seizures even in the absence of a strong familial history.[4]

Variants resulting in complete loss of function (LoF), are more commonly implicated in DS. Conversely, GEFS+ is more frequently associated with missense variants that lead to partial LoF.[5]

Key points

- FFA reduced seizures in SCN1A-related GEFS+ across a multicenter real-world cohort.
- Adjunctive FFA outperformed prior ASMs.
- Treatment efficacy may correlate with SCN1A-variant, supporting a genotype-dependent therapeutic effect of FFA.
- FFA achieved clinical benefit at low doses consistent with labeled ranges in DS routine treatment.
- FFA was well tolerated with only few and transient adverse.

Despite available antiseizure medications (ASMs), many patients with DS fail to achieve adequate seizure control. In recent years, fenfluramine (FFA), originally developed as an anti-obesity drug, has been successfully repurposed as an ASM. FFA was withdrawn from the market in 1997 due to reports of valvular heart disease and pulmonary arterial hypertension. Low-dose FFA is now

approved by various regulatory agencies for the treatment of seizures associated with DS and Lennox–Gastaut syndrome (LGS).[6,7]

Experimental studies indicate that FFA exerts its antiseizure effects by enhancing serotonergic transmission at 5-HT receptors, thereby promoting GABAergic signalling.[8] Additionally, FFA reduces glutamatergic excitability through positive modulation of sigma-1 receptors, which are implicated not only in seizure control but also in the management of nonseizure comorbidities in epileptic encephalopathies.[9]

The efficacy and safety of low-dose FFA in DS have been demonstrated in two prospective, double-blind, placebo-controlled trials.[10,11] As a result, FFA has been established among the preferred second-line therapies in the treatment algorithm for DS.[12]

Beyond its well-established efficacy in DS, FFA has also been investigated in other epileptic syndromes, including LGS, West syndrome, and CDKL5-related epilepsy, though the therapeutic response appears less pronounced than in DS. While FFA has shown strong efficacy in DS and encouraging results in other epileptic encephalopathies, its effectiveness in *SCN1A*-related epilepsies beyond DS has not yet been evaluated.

2 | METHODS

A multicenter observational investigation was conducted to assess the efficacy and tolerability of FFA in patients with *SCN1A*-related epilepsy not fulfilling criteria for DS. The study encompassed a consortium of eight specialized Neurology centers across Italy. Data collection was conducted retrospectively and continued until March 2025. A standardized case report form was used to collect anonymized clinical, instrumental, and genetic data from both inpatient and outpatient medical records. A minimum follow-up duration of 6 months after FFA initiation was required for inclusion in the analysis, in order to evaluate outcomes beyond titration and reduce short-term variability in seizure and EEG measures.

Demographic variables, including age and gender, were recorded for all patients. Baseline seizure frequency was collected from caregiver seizure diaries. Seizure types were classified in accordance with the International League Against Epilepsy (ILAE) operational classification system.[13] Genetic variants were reported following the guidelines of the American College of Medical Genetics and Genomics (ACMG). The analysis also included a review of electroencephalographic (EEG) findings before and after FFA initiation.

Descriptive statistical methods were applied to summarize demographic and clinical characteristics. Continuous variables were reported as means and ranges, while categorical variables were expressed as absolute numbers and percentages.

SCN1A missense variants were categorized based on their localization within the Nav1.1 protein and the local density of previously reported variants, following the methodology proposed by Gallagher et al.[5] Based on variant frequency ratios, three categories were established: A (variant-sparse regions), B (normal-density regions), and C (variant-dense regions).

Nonparametric statistical tests were employed to investigate potential associations between variant localization and clinical severity. Differences in age at seizure onset and seizure frequency across variant groups were assessed using the Kruskal–Wallis H test. For post hoc comparisons between groups, the Mann–Whitney U test was applied. Statistical significance was set at $p < 0.05$. Analyses were performed using Python (v.3.10).

3 | RESULTS

A total of 11 patients (7 females and 4 males) with *SCN1A*-related GEFS+ were included (Table 1).

The mean age at seizure onset was 7.2 months [4–15 months]. The baseline seizure frequency prior to FFA initiation ranged from one seizure every 2 months to several seizures per week. The clinical presentation of seizures in the cohort was heterogeneous, with a predominance of generalized motor seizures across most patients. Specifically, 9 out of 11 patients (82%) experienced generalized tonic–clonic or clonic seizures. Focal seizures were also commonly observed, occurring in six patients (55%). Absence seizures were reported in one patient, while status epilepticus was documented in another patient. Febrile seizures were recorded in 8 of 11 patients.

All patients carried missense variants, with the exception of Patient 2, who harbored a nonsense variant, and Patient 7, who carried a noncoding intronic variant. Statistical analysis did not reveal significant differences among gene variant groups in terms of age at seizure onset ($p = 0.124$) or seizure frequency ($p = 0.119$). However, pairwise comparisons revealed a trend toward significance in age at seizure onset, with lower values observed in variant C compared to variant A (median onset: 5 vs. 13 months, $p = 0.076$). Also, in terms of seizure frequency, patients carrying variant C showed a higher seizure burden compared to those with variants in groups A and B ($p = 0.059$), again suggesting a trend toward more severe phenotypes in functionally enriched regions (Figure 1).

At FFA onset, all patients were treated with VPA and 7 out of 11 cases with more than one drug without complete seizure control. FFA was introduced at a mean age of

TABLE 1 Summary of patient characteristics and response to FFA treatment.

Patient	Hospital center	Sex	Genetic variant	Variant type	Age at seizure onset (months)	Seizure frequency	Seizure type	PRE-FFA ongoing treatment	PRE-FFA suspended treatment	Age at FFA initiation (years)	FFA dose per day	FFA treatment duration (months)	Average reduction in seizure frequency with FFA	ASM modifications post FFA	Side effects	Behavioral/ cognitive changes	EEG pre FFA	EEG changes post FFA	Family history
1	ISNB	F	c.5581C>T, p.(Arg1861Trp), maternal heterozygosis	MIS	8	>1/year (6–8 per year)	Febrile and afebrile generalized tonic–clonic seizures	VPA, CLB	LEV, LTG	17.6	0.43 mg/kg (max 26 mg)	7.4	100% (7.4 months seizure free)	CLB reduction	No	More active, less drowsy	Generalized fast spike–wave discharges	Normalization	No
2	IRCCS-SR	M	c.5734C>T, p.(Arg1912Ter) heterozygosis	NS	11	>1/month (3–4 per month)	Focal and generalized, febrile and afebrile motor seizures	VPA, CLB	LCS, CBZ (pejorative), LEV	2.6	0.26 mg/kg	23.2	90% (1 seizure every 2 months, shorter duration)	No	No	No	Fronto-temporal theta/delta waves abnormalities	Normalization	No
3	OPBG	F	c.2927 T>C, p.(Met976Thr) heterozygosis de novo	MIS	4	Weekly	Febrile generalized tonic–clonic seizures	VPA	/	3.6	0.7 mg/kg	17.7	90% (1 seizure every 2 months)	VPA suspended after 9 months	No	No	Bilateral, slow posterior abnormalities	Disappearance of slow posterior abnormalities in wakefulness	No
4	IGG	F	c.5260G>A, p.(Gly1754Arg) de novo	MIS	6	Weekly	Generalized tonic–clonic seizures, sometimes triggered by light patterns or hot and cold-water induced reflex seizures	VPA, TPM, CBD, ETS	PB, LEV, CLB, STP	19	0.39 mg/kg	18.3	75% (monthly)	ETS gradual suspension, then VPA augmentation after 6 months	Temporary mild appetite reduction	Initial mild apathy, resolved with TPM suspension	Rare bursts of generalized, low-voltage, theta waves	Reduction of generalized bursts of slow waves in wakefulness	No
5	AOUM	M	c.3971 T>G, p.(Leu1324Arg)	MIS	5	Monthly	Emiclonic, focal motor seizures even prolonged, triggered by fever	STP, CLB, VPA	/	2	0.5 mg/kg	6	100% (1 febrile seizure during FFA titration, shorter and milder)	No	No	Improvement of motor aspects	Normal	No (normal)	No
6	AOUM	M	c.3693 T>A, p.(Ser1231Arg)	MIS	4	>1/month	Febrile and afebrile emiclonic and generalized tonic–clonic seizures	VPA	/	2.3	0.4 mg/kg	9.4	50–75%	No	No	No	NA	NA	No
7	AOUM	F	c.2947-5T>A, de novo	NC	4	>1/month	Febrile and afebrile generalized tonic–clonic seizures, focal motor seizures, focal nonmotor seizures	VPA	/	3.9	0.7 mg/kg	15.6	75% (>1/year, only febrile)	No	No	No	Generalized epileptiform abnormalities, with sharp/angular brief runs during drowsiness and sleep	Normalization of wake-EEG, persistence of posterior focal abnormalities in drowsiness and sleep	Mother with history of febrile seizures

TABLE 1 (Continued)

Patient	Hospital center	Sex	Genetic variant	Variant type	Age at seizure onset (months)	Seizure frequency	Seizure type	PRE-FFA ongoing treatment	PRE-FFA suspended treatment	Age at FFA initiation (years)	FFA dose per day	FFA treatment duration (months)	Average reduction in seizure frequency with FFA	ASM modifications post FFA	Side effects	Behavioral/ cognitive changes	EEG pre FFA	EEG changes post FFA	Family history
8	INCB	F	c.1144G>T, p.(Asp382Tyr) heterozygosis, de novo	MIS	6	>1/week	Febrile seizure since 1 year, then afebrile focal motor seizures with secondary generalization	TPM, VPA	CLB, LEV, LCM	19	0.21 mg/kg	7	100% (6 months seizure free)	No	Mild worsening of sleep	More active, participatory, independent	Generalized slow/ epileptiform bursts, enhanced by hyperventilation	NA	No
9	PUAG	F	c.4786C>T, p.(Arg1596Cys) heterozygosis	MIS	12	Monthly	Generalized tonic–clonic or clonic seizures, febrile and afebrile, rare focal seizures	VPA	LEV	4	0.4 mg/kg	55	Initially 75% then 100% (2 years seizure free)	No	No	No	Normal	No (normal)	No
10	SCB	M	c.2791C>T, p.(Arg931Cys) heterozygosis	MIS	5	>1/month	Febrile convulsive status epilepticus, generalized febrile and afebrile motor seizures.	VPA	/	15.3	0.2 mg/kg	20.5	100% (20.5 months seizure free)	No	No	No	Normal	No (normal)	No
11	SCB	F	c.1850_1851del-GAinsAT, p.(Arg617Asn)	MIS	15	>1/month	Generalized febrile and afebrile motor seizures, absence seizures	VPA, ETS	/	8.9	0.2 mg/kg	20.5	100% (20.5 months seizure free)	No	No	No	Normal	No (normal)	Mother, father and brother with febrile seizures, maternal grandfather with absence seizures

Abbreviations: AOUM, Azienda Ospedaliera Universitaria Meyer (Firenze, Italy); CBD, cannabidiol. CBZ, carbamazepine; CLB, clobazam; ETS, etosuccimide; GEFS+, Genetic Epilepsy with Febrile Seizures plus; IGG, Istituto Giannina Gaslini (Genova, Italy); INCB, Istituto Neurologico Carlo Besta (Milano, Italy); IRCCS-SR, IRCCS San Raffaele Roma; ISNB, Istituto delle Scienze Neurologiche di Bologna (Bologna, Italy); LCM, lacosamide; LEV, levetiracetam; OBPG, Ospedale Pediatrico Bambin Gesù (Roma, Italy); PB, phenobarbital; PUAG, Policlinico Universitario Agostino Gemelli (Roma, Italy); SCB, Spedali Civili di Brescia (Brescia, Italy); STP, stiripentol; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

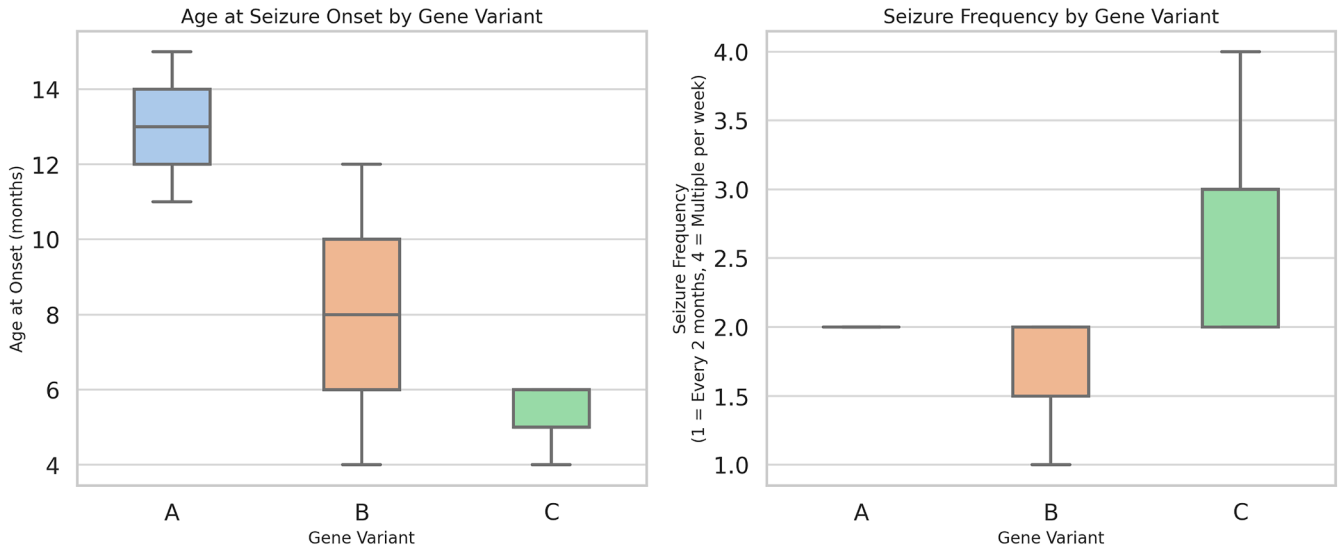

FIGURE 1 Boxplots showing the distribution of (left) age at seizure onset and (right) seizure frequency across missense variant categories. Missense variants were grouped based on their localization within the protein according to the local variant density (Variant A: sparse regions; Variant B: normal density; Variant C: variant-dense regions) according to Gallagher et al.[5] Seizure frequency was ordinally encoded (1 = every 2 months, 2 = monthly or more than once per month, 3 = weekly, 4 = more than once per week).

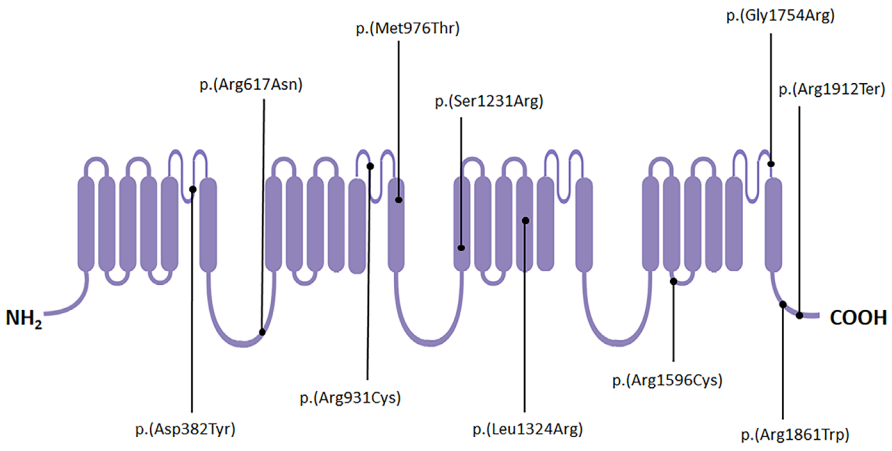

FIGURE 2 Mapping of SCN1A variants in the cohort, highlighting the locations of variants within the channel structure.

8.9 years [2–19 years] as an adjunct to ongoing ASM, following DS titration protocol. The mean FFA dosage was 0.39 mg/kg/day [0.2–0.7 mg/kg/day].

FFA resulted in an overall mean reduction of seizure frequency by 91%, with more than half (6/11) of the patients achieving complete seizure resolution. Furthermore, in 2 patients, the addition of FFA allowed for ASM tapering, with one patient discontinuing other ASMs and maintaining FFA as monotherapy. EEG follow-up was available for nine patients. Of these, five exhibited significant improvement in EEG abnormalities or complete normalization. According to parental report, besides improvements in seizure frequency, FFA was associated with enhanced alertness and behavioral responses in 3/11 patients.

At the last follow-up, the mean duration of ongoing FFA therapy was 18.2 months [6 months–4.5 years]. All patients continued FFA treatment, with no major adverse effects reported. Two patients experienced mild side effects, including transient appetite reduction and mild sleep disturbances.

4 | DISCUSSION

In this study, FFA demonstrated remarkable efficacy, leading to a significant reduction in seizure frequency across the entire cohort, with over half of the patients achieving complete seizure freedom. FFA demonstrated clinical efficacy across the full spectrum of seizure types.

This observation suggests that in *SCN1A*-related epilepsy the therapeutic benefit of FFA may extend beyond seizure classification and is effective irrespective of the epilepsy phenotype, independent of fever sensitivity. Our population exclusively comprised patients diagnosed with GEFS+ who were either nonresponsive to valproate alone or associated with other ASMs. This finding suggests that GEFS+ with *SCN1A* variants, may represent a distinct, moderately severe subgroup that is particularly responsive to FFA.

Beyond seizure reduction, FFA also led to significant improvements in EEG findings in 5/11 patients, with half of them achieving complete normalization of EEG activity, both during wakefulness and sleep.

According to caregiver reports, one-quarter of the whole cohort exhibited positive alertness and behavioral changes, a finding that is consistent with previous reports suggesting that FFA may exert additional benefits beyond seizure control. It remains uncertain to what extent the observed improvement is driven by seizure control alone or whether it also reflects a direct effect of FFA. However, these results highlight the potential broader impact of FFA on the neurobehavioral aspects of epilepsy syndromes associated with *SCN1A* variants.

Consistent with current evidence, 9/11 patients in our cohort carried missense variants. Nonsense variants are typically associated with severe LoF and more severe phenotypes, such as DS. However, in one of our patients, a nonsense variant was located in the C-terminal region of the channel (Figure 2). This finding supports the hypothesis that truncating distal mutations occurring at the end of exon 26 are associated with a milder phenotype, likely due to reduced efficiency of the nonsense-mediated mRNA decay pathway.[5] *SCN1A* missense variants tend to cluster in more central regions of the protein, particularly within the voltage sensor segment (S4) and the pore-forming domains (S5–S6). Variants located in these functional regions are more frequently associated with complete LoF and more severe phenotypes.[14] A recent study shows that DS-associated variants are more commonly found in functional domains such as the N-terminus, S4, S4–S5 linker, S5, S5–S6, and S6, while GEFS+ variants are often located in functionally less important regions like the N-terminus, S3–S4 linker, and the interdomain linkers D1–D2 and D2–D3.[5] In our cohort, missense variants showed wide variability in localization, occurring in both central and peripheral regions (Figure 2). However, although not statistically significant, likely due to the small sample size, our results show that in patients with GEFS+ missense variants located in functionally important regions were associated with a trend toward an earlier age at epilepsy onset and higher seizure frequency (Figure 1). A good clinical response to FFA was observed across all variant groups, suggesting that its efficacy is independent of the functional consequences of the underlying variant.

Although GEFS+ is classified as a self-limited epilepsy syndrome,[4] some patients are pharmacoresistant. This variability in clinical presentation has prompted our interest in exploring therapeutic options for those with drug-resistant forms of epilepsy, given the strong evidence supporting the role of FFA in *SCN1A* variants with DS phenotype.

Our results suggest that in the GEFS+ population, seizure freedom could be achieved also at lower FFA dosages with respect to DS. Unlike in DS, where higher doses (0.7 mg/kg/day) have been associated with greater efficacy,[10] we observed that a mean dose of 0.39 mg/kg/day was effective in reducing seizure frequency and EEG abnormalities. In terms of safety, FFA maintained a favorable profile across the cohort.

Our study also provides insights into the potential mechanisms of action underlying FFA's therapeutic effects. Previous studies have demonstrated the efficacy of FFA in patients with DS and other epilepsy syndromes, but the underlying reasons for the differences in response across these syndromes remain unclear. In DS, FFA has been shown to be widely effective, likely due to the homogeneity of the patient population, most of whom carry *SCN1A* pathogenic variants. By analogy, our intention with this study was to test FFA efficacy in *SCN1A*-related GEFS+, in which the functional effects of the causative *SCN1A* variants may explain a greater clinical response to FFA than to other ASMs.

Despite the small sample size, this study expands the potential therapeutic spectrum of FFA and raises important questions regarding the underlying mechanisms driving its efficacy in *SCN1A*-related epilepsies. Further research is needed to confirm these findings in larger cohorts and optimize patient selection criteria.

AUTHOR CONTRIBUTIONS

Conceptualization: FV and LG. Methodology and Clinical Case Management: GBD, AM, LG, RG, AB, NP, MP, FB, FR, AR, PS, DIB, FV. Writing—original draft preparation: GBD and AM. Writing—review and editing: GBD, AM, LG, RG, AB, NP, MP, FB, FR, AR, PS, DIB, FV. Supervision: GBD and FV. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to the contents of this study. All the authors have read the

Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of all participants involved in the study. To ensure the protection of our patients' privacy, all personal identifiers were removed from the study data.

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