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Clinical characteristics, treatment response, and prognostic factors of seizure clusters in infants and toddlers: a single-center retrospective study

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Abstract

Background

Seizure clusters (SC) are not uncommon in infants and young children; however, evidence regarding the choice of initial anti-seizure medications (ASMs) and prognostic factors remains insufficient. This study aimed to analyze the clinical characteristics, treatment response, and prognostic factors of SC in infants and young children.

Methods

We retrospectively enrolled 61 children with SC diagnosed at the Pediatric Neurology Department of Wuxi Children's Hospital between August 2020 and October 2025. The age at onset ranged from 1 to 24 months, and all children had normal development before onset. According to seizure control within 1 year of ASMs treatment, patients were divided into the effective group (seizure frequency reduction ≥ 50%) and the ineffective group (seizure frequency reduction < 50% or increased seizures). Data on age at onset, sex, personal and family history, seizure types, video-electroencephalography (VEEG), brain MRI, genetic testing, and ASMs efficacy were collected. Differences between groups were compared, and factors associated with 1-year seizure outcomes were analyzed.

Results

Among the 61 children, 50 (82.0%) were in the effective group, including 47 (77.0%) with complete seizure control; 11 (18.0%) were in the ineffective group. The age at onset was later in the effective group than in the ineffective group (9.38 ± 7.09 months vs. 4.27 ± 3.17 months, $P < 0.05$). Focal seizures were predominant in 51 patients (83.6%). Genetic testing was performed in 27 patients, and pathogenic/likely pathogenic variants were detected in 16 (59.3%), with *PRRT2* variants being the most common (8 cases). Regarding drug response, sodium channel blockers (SCBs) had the highest 1-year effectiveness rate (57.1%, 12/21). Compared with patients responding to levetiracetam, those responding to SCBs had higher proportions of VEEG abnormalities, positive family history of epilepsy/febrile seizures, and genetic variants. Warning signs for poor prognosis included abnormal brain MRI and pathogenic variants in *CDKL5*, *PCDH19*, and other refractory-related genes. Four patients developed epileptic spasms later, including 1 with a *CDKL5* variant and 3 with structural lesions.

Conclusions

The overall treatment response of SC in this infant cohort was favorable. Positive family history, *PRRT2* variants, and VEEG abnormalities may indicate priority use of SCBs; in this cohort, levetiracetam may not be the optimal first-line choice for *PRRT2*-related SC, but this requires prospective validation. The emergence of epileptic spasms, periodic cluster seizures, and structural abnormalities on brain MRI indicates poor prognosis. Structural and genetic etiologies should be actively investigated, and individualized treatments such as the ketogenic diet and surgery should be promptly considered.

Background

Seizure clusters (SC), also known as acute repetitive seizures, are a common seizure type in clinical practice. The International League Against Epilepsy has not yet established a unified definition. Commonly proposed criteria include: three or more seizures within 24 h with an interictal interval < 8 h; ≥2 seizures within 24 h; 2–4 seizures within 48 h; or two generalized seizures or three focal seizures within 4 h [1, 2]. In China, SC is defined as three or more seizures within 24 h in adults and within 12 h in children, with an interictal interval ≤ 8 h and recovery of consciousness to normal between seizures [3]. SC occurs frequently in patients with epilepsy [4] and represents a severe seizure form requiring emergency intervention, closely associated with status epilepticus, increased mortality, reduced quality of life, and increased hospitalization risk [5].

In clinical practice, non-febrile SC is commonly observed in infants and young children. When previously healthy, normally developing infants suddenly experience SC, parents often have significant anxiety, and prompt termination of seizures is clinically necessary. In addition, self-limited neonatal–infantile epilepsy syndromes often present with SC as the main manifestation, with frequent and difficult-to-control seizures at onset [6]. These syndromes are often associated with variants in *PRRT2*, *SCN2A*, *KCNQ2*, and other genes. Sodium channel blockers (SCBs) are usually the first-choice treatment and have the highest seizure-free rate in self-limited infantile epilepsy [6, 7].

For infants with sudden SC, their treatment response and whether SCBs should be the first choice remain unclear. This study retrospectively analyzed 61 infants with SC from a single center, summarizing their clinical characteristics, treatment regimens, and factors associated with 1-year outcomes, aiming to provide evidence for early identification of SC caused by non-self-limited infantile epilepsy and optimization of early treatment strategies.

Methods

Study participants and grouping

We retrospectively enrolled 61 children with SC diagnosed at the Pediatric Neurology Department of Wuxi Children's Hospital between August 2020 and October 2025. According to seizure control within 1 year of ASMs treatment, patients were divided into two groups: the effective group (seizure frequency reduction ≥ 50%) and the ineffective group (seizure frequency reduction < 50% or increased seizures). This study was approved by the Medical Ethics

Committee of Wuxi Children's Hospital (approval no. WXCH2026-04-86). Genetic testing was performed after written informed consent was obtained from the parents.

Inclusion criteria

 Age at first seizure: 1–24 months;

 Confirmed diagnosis of epilepsy, meeting the SC definition: ≥3 seizures within 12 h, interictal interval ≤ 8 h, and recovery of consciousness to normal between seizures;

 No prior use of ASMs before diagnosis, normal development, and no history of congenital defects;

 Regular follow-up for at least 1 year.

Exclusion criteria

Febrile seizures;

Presentation with status epilepticus, epileptic spasms, or myoclonic seizures at onset;

Poor treatment adherence, failure to follow medical advice, or self-reduction/discontinuation of medication leading to insufficient blood drug concentrations;

Follow-up < 1 year or incomplete clinical data.

Clinical data collection

The following data were collected: age at onset; sex; personal and family history; seizure types classified according to the 2017 ILAE operational classification of seizure types (expanded version); number of seizures at onset; magnetic resonance imaging (MRI); routine blood, urine, and stool tests and blood biochemistry; whole-exome sequencing was performed in 27 children and their parents; ASMs treatment; video-electroencephalography (VEEG): electrodes were placed according to the international 10–20 system, recording wakefulness, eye opening/closing, hyperventilation, sleep, and photic stimulation, with each recording lasting at least 4 h.

Follow-up and outcome measures

(1) Types and number of ASMs were recorded.

(2) Seizure frequency at 1 year of treatment was the primary efficacy measure: complete control: complete disappearance of clinical seizures during the 1-year follow-up; effective: seizure frequency reduction ≥ 50% from baseline; ineffective: seizure frequency reduction < 50%, no improvement, or emergence of new seizure types. Total effective rate = (number of complete control + number of effective)/total number × 100%.

(3) Drug-related adverse reactions during treatment were recorded.

(4) Recurrence, ASMs retention, emergence of epileptic spasms, and surgery during the 1-year follow-up were recorded.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. For normally distributed continuous variables, data are expressed as mean ± standard deviation (SD), and between-group comparisons were performed using independent-samples t-tests. For non-normally distributed variables, data are expressed as median (P25, P75), and between-group comparisons were performed using the Mann–Whitney U test. Categorical variables are expressed as frequency (percentage), and between-group comparisons were performed using the chi-square test, corrected chi-square test, or Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and 1-year seizure outcomes

A total of 61 full-term children with SC were enrolled. None had a history of perinatal hypoxia, head trauma, or intracranial infection, and all had normal development before onset. There were 30 boys (49.2%) and 31 girls (50.8%), with a male-to-female ratio of approximately 1:1. Within the 1-year follow-up, 50 patients (82.0%) were in the effective group, including 47 (77.0%) with complete control and 3 effective; 11 (18.0%) were in the ineffective group. The mean age at onset was 9.38 ± 7.09 months in the effective group and 4.27 ± 3.17 months in the ineffective group, with a statistically significant difference ($P < 0.05$, Table 1). Twenty patients (32.8%) had a family history of febrile seizures/epilepsy, including 18 (36.0%) in the effective group and 2 (18.2%) in the ineffective group.

Seizure types and VEEG features

Focal seizures were the predominant seizure type in 51 patients (83.6%); generalized seizures occurred in 10 patients (16.4%). VEEG revealed no significant abnormalities in 17 patients (27.9%). Focal seizures were captured in 20 patients (32.8%), while tonic–clonic seizure was documented in a single patient carrying a *PRRT2* variant. The proportion of patients with seizures captured by VEEG was higher in the ineffective group than in the effective group ($P < 0.01$, Table 1). One patient with a left temporal ganglioglioma had interictal slow waves in the left occipital region and sharp waves in the left mid-temporal region on VEEG.

Genetic testing results

Genetic testing was performed in 27 patients, and pathogenic/likely pathogenic variants were detected in 16 (59.3%). Among them, *PRRT2* variants were found in 8 patients, *CDKL5* variants in 2, *PCDH19* variants in 2, and *TBX1*, *STX1B*, *TSC2*, and *SLC2A1* variants in 1 patient each (Table 2).

Brain MRI, etiological composition of the ineffective group, and outcomes

Brain MRI abnormalities were found in 5 patients, including 2 with focal cortical dysplasia (FCD), 1 with left temporal ganglioglioma, 1 with brainstem glioma, and 1 with focal pachygyria in the right frontal lobe. All 5 patients had uncontrolled seizures within the 1-year follow-up. The patient with brainstem glioma presented with periodic cluster seizures; the 2 patients with glioma were seizure-free 1 year after surgery.

In addition to the 5 patients with structural lesions, among the 11 patients in the ineffective group, there were 2 with *CDKL5* variants, 1 with a *PCDH19* variant, 1 with a *TBX1* variant, and 2 with unknown etiology. Four patients developed epileptic spasms later with poor control, including 1 with a *CDKL5* variant and 3 with structural lesions.

Treatment response

Initial monotherapy

At 1 year of follow-up, 31 of the 50 patients in the effective group achieved effectiveness with initial monotherapy. Among them, 20 received levetiracetam, 6 received SCBs (5 lacosamide, 1 oxcarbazepine), 4 received valproate, and 1 received topiramate. Among these 31 patients, 4 had *PRRT2* variants: 2 achieved control with lacosamide, 1 with valproate, and 1 with topiramate.

Medication switching and combination therapy

The remaining 19 effective patients achieved 1-year effectiveness through medication switching or combination therapy. The main individualized pathways were as follows:

One patient with initial levetiracetam failure was found to have an *SLC2A1* variant; cerebrospinal fluid examination supported glucose transporter 1 deficiency syndrome, and seizures were controlled after adding the ketogenic diet. One patient with an *STX1B* variant achieved seizure control with levetiracetam combined with clonazepam. One patient with a *PCDH19* variant had >50% seizure reduction after combination therapy with oxcarbazepine, valproate, topiramate, and clonazepam. One patient with a *TSC2* variant showed no improvement with lacosamide, valproate, levetiracetam, or vigabatrin, but seizures were significantly reduced after adding topiramate.

Among the 6 patients with initial levetiracetam failure or levetiracetam plus topiramate failure, seizures were controlled after adding lacosamide (5 patients) or oxcarbazepine (1 patient); 3 of these patients had *PRRT2* variants, and 2 had no genetic testing but had a family history of epilepsy. One patient with a *PRRT2* variant had reduced seizures with valproate but still had seizures during fever; short-term diazepam was added during fever,then no further seizures occurred.

In addition, 4 patients with levetiracetam failure achieved seizure control after adding valproate; 2 patients with failure of both levetiracetam and oxcarbazepine achieved control after adding valproate. Among the 6 patients ultimately controlled with valproate, genetic testing was either not performed or negative. One patient with levetiracetam failure achieved control after adding topiramate. One patient with failure of levetiracetam, topiramate, and clonazepam responded to lacosamide; genetic testing was not performed.

Drug effectiveness rates

The 1-year effectiveness rates were as follows: SCBs were highest (57.1%, 12/21), followed by valproate (47.4%, 9/19), levetiracetam (44.7%, 21/47), and topiramate (13.3%, 2/15).

Comparison between levetiracetam responders and SCBs responders

Twenty-one patients who responded to levetiracetam and 12 who responded to SCBs were included. The two groups were compared regarding age at onset, sex, daily cluster seizure frequency (≥5 times), brain MRI abnormalities, VEEG abnormalities, seizures detected by VEEG, family history of epilepsy and febrile seizures, and genetic variant detection. The results showed that the SCBs responder group had higher proportions of VEEG abnormalities, positive family history of epilepsy/febrile seizures, and genetic variants than the levetiracetam responder group (Table 3).

Discussion

Clinical characteristics and factors associated with 1-year seizure outcomes in SC

In this study, the age at onset was significantly later in the effective group than in the ineffective group, suggesting that age at onset may be an important factor affecting 1-year treatment response and seizure outcomes. Previous cohort studies of infants with unprovoked cluster focal seizures reported a mean age at onset of approximately 6.2 months, with mostly benign courses [8]. Relatively later onset (e.g., approaching or exceeding 6 months) often predicts better treatment response; whereas very early onset (e.g., before 3 months) may be associated with underlying genetic or structural etiologies, increasing treatment difficulty. The mechanisms underlying this age-dependent difference remain unclear but may involve differences in brain maturity, neural network excitability, and GABAergic inhibitory function at different ages.

In this study, 32.8% of patients with SC had a family history of febrile seizures/epilepsy, with 36.0% in the effective group versus 18.2% in the ineffective group. This differs from the 61.1% family history rate reported by Lee et al. [9] in *PRRT2*-positive self-limited infantile epilepsy (SeLIE), but both suggest a potential role of genetic factors in SC. The proportion of positive family history was higher among SCBs responders. Given the close association between *PRRT2* and familial inheritance, it is speculated that patients with a positive family history may be more likely to carry benign genetic variants and respond better to targeted drugs.

In this study, 83.6% of patients with SC had focal seizures, indicating that SC is still predominantly focal. Previous studies have shown that more than half of patients with *PRRT2* variants have bilateral tonic–clonic seizures [9, 10]; however, among the 8 patients with *PRRT2* variants in this study, only 2 had generalized seizures, and the rest had focal seizures. This discrepancy may be due to phenotypic bias from the small number of *PRRT2* cases, or to VEEG improving the detection of focal seizures and reducing misclassification of focal-to-bilateral tonic–clonic seizures as generalized seizures; further validation with larger samples is needed. This study included some patients with structural lesions, whose seizures also predominantly had focal onset, consistent with Saito et al. [11] reporting that FCD-related epilepsy is characterized by focal seizures, further supporting focal seizures as an important clinical clue for identifying structural etiologies. The proportion of seizures detected by VEEG was higher in the ineffective group than in the effective group, especially in patients with structural lesions, suggesting that structural etiologies are closely associated with more active epileptiform activity and poorer 1-year outcomes. In addition, SCBs responders had a higher proportion of VEEG abnormalities and genetic abnormalities than levetiracetam responders, suggesting that VEEG abnormalities may be more prominent in patients with genetic etiologies, which may help guide clinical drug selection.

In this study, all 4 patients who developed epileptic spasms later had poor seizure control; 1 had a *CDKL5* variant and 3 had structural lesions. This is consistent with Wong et al. [12] reporting that *CDKL5* deficiency disorder often presents with refractory epilepsy and epileptic spasms, suggesting that the emergence of epileptic spasms may be an important warning sign of poor 1-year outcomes in SC and requires timely etiological investigation and treatment adjustment. In addition, all 5 patients with abnormal brain MRI had ASMs treatment failure; the patient with brainstem glioma presented with periodic cluster seizures, which closely matches the typical periodic cycle of seizure clustering and suppression reported by Saito et al. [11] in patients with FCD. This suggests that periodic cluster seizures may serve as an important clinical warning sign of underlying structural brain lesions; structural abnormalities are also key risk factors for treatment failure and poor 1-year outcomes in SC.

Genetic testing results and clinical significance in SC

Among the 27 patients who underwent genetic testing in this study, 16 (59.3%) had pathogenic/likely pathogenic variants, which may be related to the inclusion of patients without clear perinatal abnormalities, who were more likely to have genetic etiologies. In terms of gene distribution, *PRRT2* variants were most common (8 patients, 50.0% of detected variants), followed by *CDKL5* and *PCDH19* (2 each), and *TBX1*, *STX1B*, *TSC2*, and *SLC2A1* (1 each). This spectrum is consistent with Lee et al. [9] reporting *PRRT2* as a core pathogenic gene in SeLIE.

Regarding treatment response, patients with *PRRT2* variants generally had favorable outcomes: in this study, 4 patients achieved seizure control with lacosamide, valproate, or topiramate, and another patient had only occasional seizures during fever with valproate, which resolved after adding diazepam, confirming that *PRRT2*-related SC is sensitive to multiple ASMs. We also found that SCBs responders had higher proportions of genetic variants and positive family history, which is related to the predominance of *PRRT2* variants in this study; moreover, 3 patients with *PRRT2* variants had poor initial response to levetiracetam but achieved control after switching to lacosamide or oxcarbazepine, consistent with previous literature [13], further suggesting that levetiracetam may not be the optimal first-line ASM for *PRRT2*-related SC.

CDKL5 regulates neuronal development and synaptic plasticity, and its variants can cause severe neurodevelopmental disorders and refractory epilepsy. In this study, both patients with *CDKL5* variants were in the ineffective group, suggesting that CDKL5 variants are important genetic factors for treatment failure in SC. *PCDH19* variants are mainly associated with epilepsy in females. Among the 2 patients with *PCDH19* variants in this study, 1 was in the ineffective group, and 1 had > 50% seizure reduction after multidrug combination therapy, suggesting heterogeneity in treatment response of *PCDH19*-related SC, consistent with Kowkabi et al. [14].

SLC2A1 encodes glucose transporter 1, and its variants can cause glucose transporter 1 deficiency syndrome, leading to epileptic seizures due to insufficient brain energy supply. In this study, 1 patient with an SLC2A1 variant failed levetiracetam monotherapy but achieved seizure control after adding the ketogenic diet, confirming the targeted therapeutic value of the ketogenic diet for *SLC2A1*-related epilepsy. *TSC2* variants can cause tuberous sclerosis complex, and neurological involvement often manifests as refractory epilepsy. In this study, 1 patient with a *TSC2* variant showed no improvement with multiple ASMs but had reduced seizures after adding topiramate, suggesting that topiramate may have targeted efficacy for *TSC*-related SC, consistent with previous literature [15].

Treatment strategies and drug efficacy analysis in SC

Initial treatment and drug selection

In this study, 31 patients achieved effectiveness with initial monotherapy, and levetiracetam was the most commonly selected first-line drug. Levetiracetam is often preferred as first-line monotherapy because of its good tolerability, low incidence of adverse reactions, and rapid titration[16]. In this study, the 1-year effectiveness rate of levetiracetam was 44.7%, lower than that of SCBs and valproate. However, 1 patient with an *STX1B* variant achieved seizure control with levetiracetam combined with clonazepam, suggesting that levetiracetam may still be effective in some patients with specific genetic variants [17].

In this study, SCBs had the highest 1-year effectiveness rate (57.1%, 12/21), consistent with previous reports that SCBs have the highest seizure-free rate in patients with SeLIE [7], especially in patients with *PRRT2* variants. The mechanism may involve the negative regulatory effect of *PRRT2* protein on sodium channels: *PRRT2* variants lead to abnormal sodium channel activation, and SCBs can inhibit neuronal hyperexcitability by blocking abnormal sodium currents [18]. In this study, SCBs responders had higher proportions of family history of epilepsy/febrile seizures and genetic variants than levetiracetam responders, further supporting the targeted efficacy of SCBs in patients with genetic etiologies, although this comparison was non-randomized and requires prospective validation.

Valproate, as a broad-spectrum ASM, had a 1-year effectiveness rate of 47.4% in this study, especially in patients without genetic testing or with negative genetic results; all 6 patients ultimately controlled with valproate had no clear pathogenic genes, consistent with Romoli et al. [19] reporting that valproate exerts broad-spectrum anti-seizure effects by enhancing GABAergic inhibition and blocking multiple ion channels. In addition, valproate also had some efficacy in patients with *PRRT2* variants; 1 patient with a *PRRT2* variant had reduced seizures with valproate and only occasional seizures during fever, which were completely controlled after adding diazepam, suggesting that valproate can be an alternative drug for *PRRT2*-related SC.

Combination therapy and individualized regimens

For patients with initial monotherapy failure, actively identifying the etiology and switching or combining drugs is an important strategy. In this study, 4 patients with initial levetiracetam failure achieved control after adding lacosamide, including 3 with *PRRT2* variants. One patient with an *SLC2A1* variant failed levetiracetam monotherapy but achieved control after adding the ketogenic diet. One patient with a *PCDH19* variant had > 50% seizure reduction after multidrug combination therapy with oxcarbazepine, valproate, topiramate, and clonazepam, consistent with Kowkabi et al. [14] reporting that *PCDH19*-related epilepsy often requires multidrug combination therapy. In addition, 2 patients with glioma were seizure-free after surgery, suggesting that surgery can be an important option for SC patients with definite structural lesions after drug failure, consistent with Granados et al. [20] proposing that epilepsy related to structural lesions should be evaluated for surgery as early as possible.

Limitations and future perspectives

This study has several limitations. First, the sample size was relatively limited, and this was a single-center retrospective study, which may have introduced selection bias. Second, drug comparisons were non-randomized and based on drug exposure episodes, with confounding by indication, so direct comparisons of drug efficacy cannot be made. Third, genetic testing covered only part of the patients and may have missed some pathogenic genes. Fourth, the follow-up duration was only 1 year, so long-term prognosis cannot be evaluated. Future studies should expand the sample size, conduct prospective multicenter studies, and extend follow-up to 2–5 years to further clarify the long-term prognosis and gene–phenotype–efficacy relationships in SC.

Conclusions

The 1-year treatment response of children with SC in this cohort was generally favorable (complete control rate 77.0%). The age at onset was significantly later in the effective group than in the ineffective group, suggesting that age at onset may be an important predictor of 1-year seizure outcomes. The genetic testing positivity rate was 59.3%, with *PRRT2* variants being the most common. Regarding treatment, SCBs had the highest 1-year effectiveness rate (57.1%), superior to levetiracetam (44.7%) and valproate (47.4%), but this comparison was a non-randomized exploratory analysis. Clinical indications for prioritizing SCBs may include positive family history, detection of sensitive genetic variants such as *PRRT2*, and VEEG abnormalities; such patients respond better to SCBs. In this cohort, levetiracetam should not be the first choice for *PRRT2*-related SC, but prospective validation is needed. For previously healthy infants with SC, if initial SCBs treatment is ineffective or warning signs such as later epileptic spasms and periodic cluster seizures appear, structural and genetic etiologies should be actively investigated, and individualized treatments such as the ketogenic diet and surgery should be promptly adopted.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The datasets used during the current study are not publicly available due to protect patient privacy but are available from the corresponding author on reasonable request.

Human Ethics and Consent to Participate declarations: This study was approved by the Medical Ethics Committee of Wuxi Children's Hospital (approval no. WXCH2026-04-86). The ethics committee waived the requirement for informed consent from the legal guardians of the participants because of the retrospective design, use of de-identified clinical data, and minimal risk to the subjects. All procedures were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable. No individual-level identifiable data, photographs or case details that could identify any infant or toddler are presented in this manuscript.

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Authors' contributions

Xiaoyue Hu: conceptualization, study design, patient enrollment and clinical data collection, data analysis, and writing of the original draft. **Miao Jing**: patient enrollment, clinical data collection, follow-up assessment, and data curation.

Yangping Wang: patient enrollment, clinical data collection, follow-up assessment, and validation.

Jianbiao Wang: genetic data analysis, statistical analysis, and interpretation of results.

Ying Hua: conceptualization, supervision, funding acquisition, and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

References

1. Cloyd J, Haut S, Carrazana E, et al. Overcoming the challenges of developing an intranasal diazepam rescue therapy for the treatment of seizure clusters. Epilepsia. 2021;62(4):846–56.
2. Jafarpour S, Hirsch LJ, Gainza-Lein M, et al. Seizure cluster: definition, prevalence, consequences, and management. Seizure. 2019;68:9–15.
3. Chinese Medical Association. Clinical diagnosis and treatment guidelines: epilepsy volume. Beijing: People's Medical Publishing House; 2022.
4. Haut SR. Seizure clustering. Epilepsy Behav. 2006;8(1):50–5.
5. Morris GL 3rd, Eads P, Tryfon M, et al. Seizure clusters, treatment patterns, and healthcare resource utilization in patients with epilepsy: a Wisconsin-based claims analysis. Epilepsy Behav. 2024;157:109867.
6. Zuberi SM, Wirrell E, Yozawitz E, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63(6):1349–97.
7. Sari Yanartas M, Donbaloglu F, Genc S, et al. What is the right choice? Is the answer sodium channel blockers? Epileptic Disord. 2025;00(0):1–11.
8. van Roest A, Van de Vel A, Lederer D, et al. The clinical and genetic spectrum in infants with (an) unprovoked cluster(s) of focal seizures. Eur J Paediatr Neurol. 2020;24:148–53.
9. Lee J, Kim YO, Lim BC, et al. PRRT2-positive self-limited infantile epilepsy: initial seizure characteristics and response to sodium channel blockers. Epilepsia Open. 2023;8(2):436–43.
10. Komar M, Sidhu J, Joseph J, et al. PRRT2-related epilepsy: from self-limited infantile epilepsy to atypical epilepsy phenotypes. Neurol Genet. 2025;11(3):e200267.
11. Saito Y, Sugai K, Iwasaki M, et al. Periodic cycles of seizure clustering and suppression in children with epilepsy strongly suggest focal cortical dysplasia. Dev Med Child Neurol. 2023;65(3):431–6.
12. Wong H, Ishii H, Paterson E, et al. CDKL5 deficiency disorder-related epilepsy: a review of current and emerging treatment. CNS Drugs. 2022;36(6):591–604.
13. Tian Y, Shi Z, Cai JH, et al. Levetiracetam may be an unsuitable choice for patients with PRRT2-associated self-limited infantile epilepsy. BMC Pediatr. 2023;23:529.
14. Kowkabi S, Yavarian M, Kaboodkhani R, et al. PCDH19-clustering epilepsy, pathophysiology and clinical significance. Epilepsy Behav. 2024;154:109730.
15. Liu XC, Zhang YF, Hao YP, et al. Tuberous sclerosis complex presenting as convulsive status epilepticus followed by hypoxic cerebropathy: a case report. Med (Baltim). 2019;98(19):e15545.
16. Latif Z, Mukhtar M, Rohan A, et al. Comparison of levetiracetam versus sodium valproate as a monotherapy in early childhood epilepsy. Cureus. 2025;17(7):e87574.
17. Tian Y, Hou C, Wang XY, et al. A novel inherited STX1B mutation associated with generalized epilepsy with febrile seizures plus: a family analysis and literature review. Zhonghua Er Ke Za Zhi. 2019;57(3):206–10.
18. Fruscione F, Valente P, Sterlini B, et al. PRRT2 controls neuronal excitability by negatively modulating Na+ channel 1.2/1.6 activity. Brain. 2018;141(4):1000–16.
19. Romoli M, Mazzocchetti P, D'Alonzo R, et al. Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. Curr Neuropharmacol. 2019;17(10):926–46.
20. Granados AM, Orejuela JF, Rodriguez-Takeuchi SY. Neuroimaging evaluation in refractory epilepsy. Neuroradiol J. 2015;28(6):529–35.

Tables

Table 1 Comparison of clinical characteristics between the effective and ineffective groups

Characteristic	Effective group (n = 50)	Ineffective group (n = 11)	P value
Sex, male	25	5	0.785
Age, years	9.38±7.09	4.27±3.17	**0.001**
High seizure frequency (≥5/day)	23	8	0.108
MRI abnormality	0	5	**0**
EEG abnormality	33	11	0.057
Seizures captured on EEG monitoring	13	8	**0.009**
Family history of epilepsy / febrile seizures	18	2	0.432
Genetic variant identified	12	4	0.642

EEG, electroencephalography; MRI, magnetic resonance imaging

Table 2 Genetic variants, clinical characteristics, ASM regimens and 1-year outcomes in children with SC undergoing genetic testing

No.	Sex	Gene (RefSeq)	Nucleotide change	Protein change	Origin	ACMG	Family history	Onset (mo)	Seizure types	ASMs	Prognosis
1	M	PRRT2	Whole gene deletion (16p11.2)	p.?	de novo	P	Cousin had epilepsy	4	Focal	LCM	Good
2	F	PRRT2	c.649dupC	p.R217Pfs*8	Father	P	Older brother had epilepsy	8	Focal	LCM	Good
3	F	PRRT2	c.649dupC	p.R217Pfs*8	Mother	P	Older brother had epilepsy	8	Focal	TPM	Good
4	F	PRRT2	c.236C>T	p.S79L	Father	LP	None	19	Generalized	VPA	Good
5	M	PRRT2	c.649dupC	p.R217Pfs*8	Mother	P	Mother had epilepsy	5	Focal	LEV → LCM	Good
6	F	PRRT2	c.641dupC	p.A214fs*13	Mother	P	None	3	Focal	LEV → OXC	Good
7	M	PRRT2	c.641dupC	p.A214fs*13	Father	P	Father had febrile seizures	4	Focal	TPM; LEV → OXC	Good
8	F	PRRT2	c.797G>A	p.R266Q	Mother	LP	None	18	Generalized	VPA; DZP (during fever)	Good
9	M	TSC2	c.3737_3738del	p.D1246fs*22	Mother	LP	None	12	Focal	LCM, VPA, LEV, VGB, TPM	Seizure reduction
10	F	CDKL5	c.592G>A	p.G198S	de novo	LP	None	2	Focal →epileptic spasms	LEV, OXC, VPA, LTG, VGB, TPM	Uncontrolled epilepsy
11	M	CDKL5	c.1553delC	p.P518Hfs*5	de novo	P	None	1	Focal	LEV, TPM	Uncontrolled epilepsy
12	M	PCDH19	Whole exon 3 deletion	p.?	de novo	P	None	11	Focal	LEV, VPA, TPM, NZP	Uncontrolled epilepsy
13	M	PCDH19	c.1031C>T	p.P344L	de novo	LP	None	8	Focal	OXC, VPA, TPM, NZP	Seizure reduction
14	F	SLC2A1	Whole gene deletion (1p34.2)	p.?	de novo	P	None	1	Generalized	LEV → KD	Good
15	M	TBX1	Whole gene deletion (22q11.21)	p.?	de novo	P	Older sister had febrile seizures	6	Focal	LEV, TPM	Controlled seizures
16	M	STX1B	c.445C>T	p.Q149*	Father	LP	None	23	Focal	LEV, CZP	Good

ACMG, American College of Medical Genetics and Genomics classification (P, pathogenic; LP, likely pathogenic). ASMs, anti-seizure medications: LEV, levetiracetam; LCM, lacosamide; OXC, oxcarbazepine; VPA, valproate; TPM, topiramate; CZP, clonazepam; DZP, diazepam; LTG, lamotrigine; NZP, nitrazepam; VGB, vigabatrin; KD, ketogenic diet. mo, months; M, male; F, female. Arrows (→) indicate sequential add-on or switch therapy

Table 3 Baseline clinical characteristics of children with SC in the LEV-effective group versus the SCBs-effective group

Characteristic	LEV-effective (n = 21)	SCBs-effective (n = 12)	P value
Sex, male	9	7	0.481
Age, years	8.52 ± 8.00	6.25 ± 3.00	0.253
High seizure frequency (≥5/day)	10	8	0.469
MRI abnormality	0	0	1.000
EEG abnormality	7	9	**0.032**
Seizures captured on EEG monitoring	6	6	0.274
Family history of epilepsy / febrile seizures	5	8	**0.027**
Genetic variant identified	1	5	**0.016**

SC, seizure clusters; LEV, levetiracetam; SCBs, sodium channel blockers; EEG, electroencephalography; MRI, magnetic resonance imaging

Figures

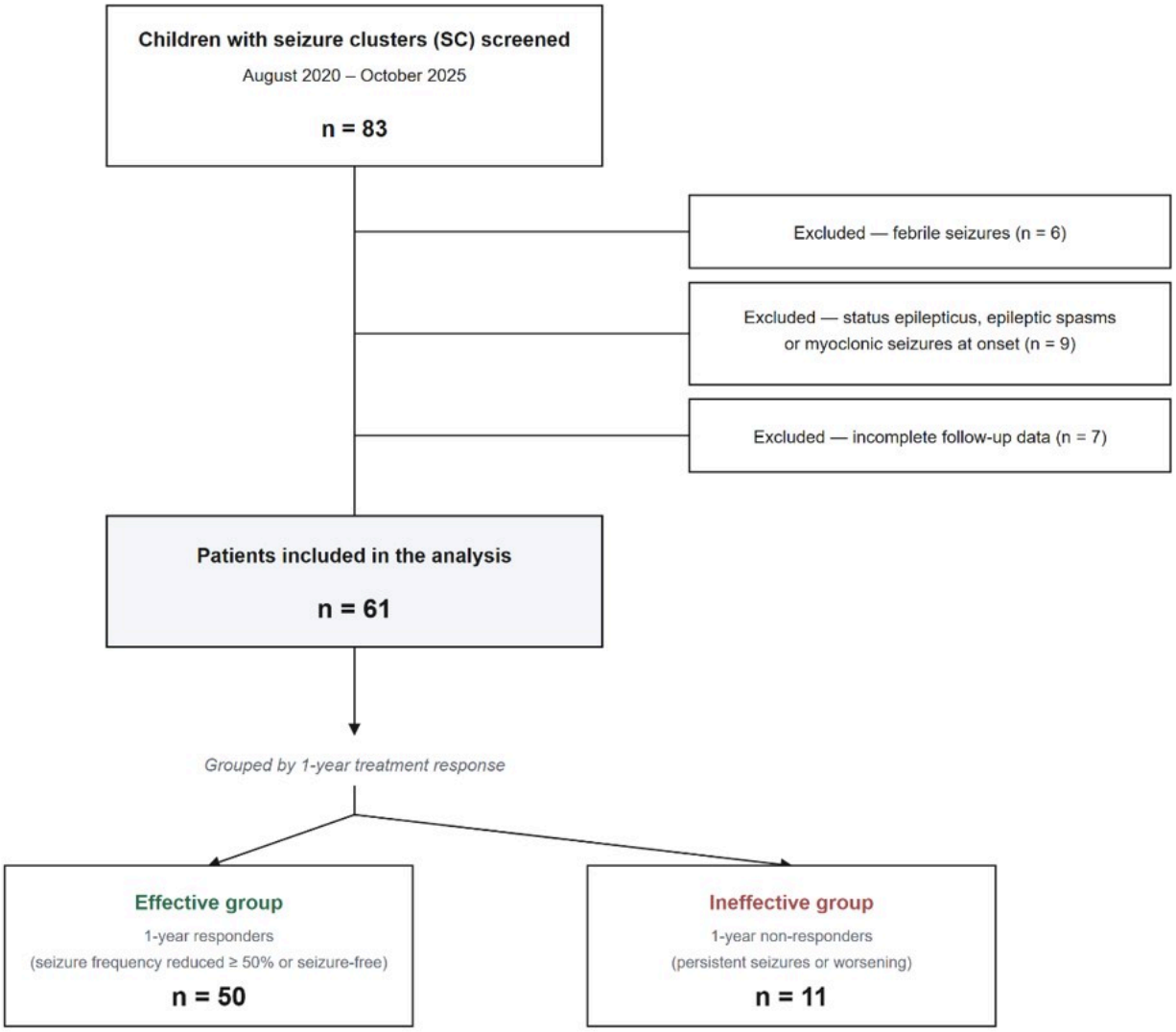

Figure 1

Flowchart of patient enrollment and follow-up