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The effect of early therapy on school achievement in children with Self-limited Epilepsy with Centrotemporal Spikes

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Research Article

Keywords: Self-limited Epilepsy with Centrotemporal Spikes, spike wave index, school achievement, interictal epileptiform discharges, antiseizure medicine

Posted Date: March 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8719402/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

This study aimed to evaluate academic performance in children diagnosed with Self-limited Epilepsy with Centrotemporal Spikes (SeLECTS). Additionally, it sought to analyze the impact of early antiseizure medicine (ASM) therapy initiation on both academic outcomes and seizure control in pediatric SeLECTS patients.

Patients and Methods:

This retrospective study examined 107 children with SeLECTS admitted to the Epilepsy Center of Jinan Children's Hospital from May 2019 to July 2022. Inclusion criteria required children to be over 8 years old at final follow-up and have undergone medication for a minimum of two years. The spike wave index (SWI) was calculated by summing spikes during 5 minutes of drowsiness and Non-REM stage 2 sleep, with analysis conducted in two groups: ≥ 50% and < 50%. EEG improvement, based on SWI% resolution, was categorized as good response (≥ 50% decrease in SWI) or poor response (< 50% decrease in SWI), determined through two-year sequential follow-up EEG recordings compared to baseline. School achievement was evaluated using standardized Primary and Secondary School Achievement Tests in China.

Results

All cases had more than 2 years of follow-up, and 94 children (87.9%) were seizure-free. All children completed the Primary and Secondary School Achievement Tests, with 64 (59.8%) children displaying high achievement (score ≥ 70) and 43 (40.2%) children displaying low achievement (score < 70) on the most recent test. The factors significantly associated ($p < 0.05$) with scores were the number of ASMs and seizure numbers before treatment. Children who experienced more seizures before treatment (≥ 5) and had lower SWI reduction (≤ 50%) demonstrated poorer seizure outcomes. Older onset age correlated with a good response in SWI reduction (> 50%). In multivariate logistic regression analysis, only seizure numbers before treatment were significantly associated with school achievement.

Conclusions

This study emphasizes the significance of initiating ASM therapy early in children diagnosed with SeLECTS. The results underscore the necessity for a tailored treatment approach, considering both clinical manifestations and electroencephalogram (EEG) characteristics to enhance outcomes for pediatric patients with SeLECTS.

Introductions

Self-limited Epilepsy with Centrotemporal Spikes (SeLECTS), formerly known as Benign childhood Epilepsy with Centrotemporal Spikes (BECTS), was the most prevalent epilepsy syndromes in children and is characterized by seizure remission[1]. The onset age for SeLECTS typically ranges from 3 to 14 years, with seizures resolving by ages 15 to 17 years [2]. In China, the mean age of onset was reported as 6.85 years [3]. Recent research has revealed learning difficulties and subtle cognitive dysfunction in children with SeLECTS [4]. Given its typical diagnosis in early school-aged children, SeLECTS may significantly impact academic achievement [5]. Children with SeLECTS have demonstrated specific cognitive deficits primarily affecting language, visuospatial abilities, and attention [6]. Consequently, the International League Against Epilepsy (ILAE) has replaced the term "benign" with "self-limited" in its latest 2022 definition [1]. An EEG-fMRI study indicated that interictal rolandic spikes directly disrupt functional brain networks responsible for language, behavior, and cognition in children with SeLECTS [7]. This disruption was associated with a brief, interrupting impact on the inferior parietal lobe and adjacent parietal areas.

A small proportion of children originally diagnosed with SeLECTS may be refractory to antiseizure medicine (ASM), potentially progressing to epileptic encephalopathy. In the case of encephalopathy related to Status Epilepticus during slow Sleep (ESES), there was a clear link between cognition and interictal epileptiform discharges (IEDs) [8].

The spike wave index (SWI) quantifies epileptiform activity in the electroencephalogram (EEG) during the non-rapid eye movement (NREM) sleep phase. A recent study demonstrated that children with SeLECTS and higher SWI perform significantly worse on arithmetic calculations and memory tests compared to those with lower SWI [9]. Monotherapy has been shown to be statistically more effective in spike reduction compared to combination therapies [10]. However, previous studies have indicated that ASM treatment did not affect EEG normalization [11]. Other studies have reported opposing evidence that finds no correlation between IEDs and neuropsychological outcome[12].

To the best of our knowledge, there were limited studies evaluating the effects of baseline EEG features, clinical characteristics, and ASM on academic performance in children with SeLECTS. This study retrospectively analyzed seizure characteristics, EEG patterns, treatment, and outcomes in a cohort of children diagnosed with SeLECTS. The primary objectives of our research were to quantify the prevalence of SWI in children with SeLECTS and to examine the impact of early ASM therapy initiation on both academic performance and seizure outcomes in this patient population.

Patients and Methods

Patient selection

This retrospective observational study included patients with SeLECTS admitted to the Epilepsy Center of Jinan Children's Hospital from May 2019 to July 2022. SeLECTS diagnosis was based on the ILAE

guidelines [13]. The study included only patients who underwent 24-hour video EEG recording with sleep recording signals (two electrooculographic channels and the mentalis electromyographic channel). At the final follow-up, children were required to be over 8 years old and have been on medication for at least two years. Epilepsy outcome, assessed at the last follow-up visit, classified seizure freedom as no seizures for more than one year. Exclusion criteria were: (a) patients with metal implants (e.g., vagus nerve stimulation), (b) patients with a history of other neurological or psychiatric disorders, including traumatic brain injury and schizophrenia, and (c) patients with significant growth retardation.

The study gathered demographic and clinical data from patients, encompassing information on sex, age, seizure outcomes, and ASM usage. Analysis focused on seizures observed by parents or caregivers and subsequently reported during outpatient visits.

EEG recordings and pre-processing

Scalp EEG recordings were conducted using a 32-channel digital EEG system with electrodes placed according to the international 10–20 system. Both sleep and waking EEGs were recorded. Centrotemporal spikes were visually quantified on each sleep EEG recording, and their occurrence during non-rapid eye movement (non-REM) sleep was assessed to measure the SWI. SWI was analyzed with the percentage of spikes in the 5 minutes epoch in NREM sleep EEG recording. Each 10-s page was evaluated in detail to calculate the SWI. The number of seconds containing one or more spikes and wave discharges was recorded as a number (0–10). At the end of the first 5 minutes, the number of seconds with epileptiform discharges was divided by the total number of seconds in the epoch and multiplied by 100 to reflect the results as a percentage[8]. The first and last EEGs of the patients were evaluated in terms of SWI and lateralization. The data were reviewed by two EEG readers.

The SWI was analyzed in two groups: ≥50% and < 50%. EEG improvement with SWI resolution was categorized as good response (a decrease of ≥ 50% in SWI) or poor response (a decrease of < 50% in SWI) based on two-year sequential follow-up EEG recordings compared with baseline. A unilateral pattern was determined if both ipsilateral electrode chains were involved and the contralateral hemisphere pattern was < 50% in amplitude. A bilateral pattern was identified if the initial EEG change was bi-hemispheric and diffuse.

Antiseizure medication

ASM therapy was initiated in patients who experienced two or more seizures. Add-on therapy with ASM (dual therapy or polytherapy) was administered if seizure frequency persisted despite the administration of a full dose of the initial drug. The cohort was subsequently divided into two groups: (1) monotherapy and (2) dual therapy or polytherapy.

School achievement tests

Primary and secondary school achievement tests (final exam) comprise various subtests, include tests of reading, vocabulary, and mathematics, yielding a total Composite score that serves as a measure of overall academic performance. The test results show a high degree of consistency within one county and city. The content of these tests remains largely consistent across grade levels, with scores typically demonstrating high correlation. Given these characteristics, the tests were considered interchangeable and reflective of students' characteristic achievement levels. Based on their scores, subjects were categorized into two groups: a high achievement group (scores ≥ 70) and a low achievement group (scores < 70).

Statistical analysis

Statistical analysis was conducted using SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were described using mean and standard deviation (SD). Fisher's exact test was employed to analyze sex, seizure frequency, EEG pattern, SWI before treatment, ASM numbers, and SWI change. An Analysis of Variance (ANOVA) was utilized for comparing age at onset. Statistical significance was defined as $P < 0.05$. A multivariate logistic regression model was applied. Results were considered statistically significant at the 5% level ($P < 0.05$).

Results

The study included 107 children (Fig. 1) (66 boys and 41 girls). The mean age at epilepsy onset was 8.08 years (range 4–15 years). All cases had more than 2 years of follow-up, and 94 children (87.9%) became seizure-free; no participants were lost to follow-up. At the last follow-up, 73 (68.2%) children were using only one ASM. Prior to treatment, 46 (42.9%) children experienced more than 5 seizures. All seizures were were described by witnesses, there was no clearly clarification for the seizure semiology. The most common ASM at the time of the treatment was levetiracetam (LEV) (n = 47), followed by oxcarbazepine (OXC) (n = 21) (Table 1).

Table 1
Patient characteristics and school achievement (n = 107)

Characteristics	All patients	high achievement	low achievement	*P* value
	N = 107	N = 64	N = 43	
Sex, female: male	41:66	26:38	15:28	0.347
Age at onset, Mean ± SD, years	8.08 ± 2.33	8.29 ± 2.43	7.76 ± 2.17	0.252
Number of ASMs				
=1	73	50	23	0.007#
>1	34	14	20	
ASM used				
OXC	21	15	6	0.313
LEV	47	27	20	
Others	39	22	17	
Age onset group				
≤8 years	56	30	26	0.118
>8 years	51	34	17	
SWI before treatment				
≤50%	78	47	31	0.525
>50%	29	17	12	
SWI change				
≤50%	60	35	25	0.439
>50%	47	29	18	
IEDs pattern				
Unilateral pattern	53	31	22	0.468
Bilateral pattern	54	33	21	
SZ Outcome				
SZ free	94	59	35	0.086
No SZ free	13	5	8	

Legends: ASM=antiseizure medicine;DEE=developmental and epileptic encephalopathy; IEDs=interictal epileptiform discharges; LEV, levetiracetam; OXC, oxcarbazepine□SWI=spike wave index; SZ, seizure

Characteristics	All patients N = 107	high achievement N = 64	low achievement N = 43	*P* value
SZ numbers before treatment				
≤2	29	20	9	0.014#
2–5	32	24	8	
>5	46	20	26	

Legends: ASM=antiseizure medicine;DEE=developmental and epileptic encephalopathy; IEDs=interictal epileptiform discharges; LEV, levetiracetam; OXC, oxcarbazepine□SWI=spike wave index; SZ, seizure

All children completed the Primary and Secondary School Achievement Tests, with 64 (59.8%) children demonstrating high achievement (score ≥ 70) and 43 (40.2%) children showing low achievement (score < 70) on the most recent test. An unilateral EEG pattern was observed in 53 (49.5%) children. 60 (56.1%) children experienced a reduction in SWI of more than 50%.

Sex and age of onset were not significant predictors of performance on measures of academic achievement in univariable analysis. No significant differences were observed regarding the age of epilepsy onset, IEDs pattern, ASMs used, SWI before treatment, and SWI change. Factors significantly associated ($p < 0.05$) with scores included the number of ASMs and seizure numbers before treatment (Table 1).

The number of ASMs, the type of ASMs and SWI before treatment were not significant predictors of seizure outcome. Factors significantly associated ($p < 0.05$) with seizure outcome are SWI change, seizure numbers before treatment and age at last follow up. Children who had more seizures before treatment (≥ 5) and had lower SWI reduction (≤ 50%) demonstrated poor seizure outcomes. Older children significantly associated ($p = 0.011$) with seizure outcome. The age of onset may be significantly associated ($p = 0.053$) with seizure outcome (Table 1 and 2).

Table 2
Patient characteristics and seizure outcome (n = 107)

Characteristics	All patients N = 107	SZ free N = 94	No SZ free N = 13	*P* value
Sex				
Female	66	60	6	0.177
Male	41	34	7	
Number of ASMs				
=1	73	67	6	0.069
>1	34	27	7	
ASM used				
OXC	21	18	3	0.467
LEV	47	44	3	
Others	39	32	7	
Age onset				
≤8 years	56	46	10	0.053
>8 years	51	48	3	
Age at last follow up				
<10 years	49	38	11	0.009#
10-12years	30	29	1	
13-15years	23	22	1	
>15 years	5	5	0	
SWI before treatment				
≤50%	78	68	10	0.510
>50%	29	26	3	
SWI change				
≤50%	60	57	3	0.012#
>50%	47	37	10	
IEDs pattern				

Legends: ASM=antiseizure medicine; IEDs=interictal epileptiform discharges; LEV, levetiracetam; OXC, oxcarbazepine;SWI=spike wave index; SZ=seizure;

Characteristics	All patients N = 107	SZ free N = 94	No SZ free N = 13	*P* value
Unilateral pattern	53	46	7	0.485
Bilateral pattern	54	48	6	
SZ numbers before treatment				
≤2	29	28	1	0.004#
2–5	32	31	1	
>5	46	35	11	
Legends: ASM=antiseizure medicine; IEDs=interictal epileptiform discharges; LEV, levetiracetam; OXC, oxcarbazepine;SWI=spike wave index; SZ=seizure;				

The number of ASMs, SWI before treatment, and IEDs pattern were not significant predictors of changes in SWI on univariable analysis. The factors significantly associated ($p < 0.05$) with SWI change were age of onset and age at last follow up. Older onset age and older children correlated with a favorable response in SWI reduction (> 50%) (Table 3).

Table 3
Patient characteristics and SWI change (n = 107)

Characteristics	All patients N = 107	SWI reduce > 50% N = 60	SWI reduce ≤50% N = 47	*P* value
Sex				
Female	66	39	27	0.275
Male	41	21	20	
Number of ASMs				
=1	73	44	29	0.142
>1	34	16	18	
Age onset				
≤8 years	56	24	32	0.003#
>8 years	51	36	15	
Age at last follow up				
<10 years	49	22	27	0.011#
10-12years	30	18	12	
13-15years	23	15	8	
>15 years	5	5	0	
SWI before treatment				
≤50%	78	41	37	0.163
>50%	29	19	10	
IEDs pattern				
Unilateral pattern	53	34	19	0.485
Bilateral pattern	54	26	28	
SZ numbers before treatment				
≤2	29	18	11	0.701
2–5	32	18	14	
>5	46	24	22	

Legends: ASM=antiseizure medicine; IEDs=interictal epileptiform discharges; SWI=spike wave index; SZ=seizure;

The multivariate logistic regression analysis revealed that only the frequency of seizures prior to treatment demonstrated a significant association with academic performance (Table 4).

Table 4
Multivariate analysis predictors of school achievement

Predictor	P value	Exp(B)	95% CI
Sex Female vs. Male	0.340	0.645	0.262–1.588
Age onset ≤ 8 years vs. >8 years	0.236	0.586	0.242–1.420
SWI before treatment > 50% vs. ≤50%	0.796	1.138	0.427–3.031
IEDs pattern Unilateral vs. Bilateral	0.691	0.838	0.349–2.009
Number of ASMs = 1 vs. >1	0.061	2.468	0.959–6.346
SWI change ≤50% vs. >50%	0.263	0..581	0.225–1.503
SZ Outcome SZ free vs. No SZ free	0.433	1.727	0.441–6.768
SZ numbers before treatment ≤5 vs. >5	0..039#	2.635	1.050–6.617
Legend: vs. = versus; CI = confidence interval; ASM=antiseizure medicine; IEDs=interictal epileptiform discharges; SWI=spike wave index; SZ=seizure;			

Discussion

SeLECTS was the most prevalent focal epilepsy syndrome, accounting for 8–25% of childhood epilepsies with an overall incidence of 10–20:100,000 in children [14]. This syndrome typically has a favorable prognosis, with spontaneous remission expected around 12 to 13 years of age, prior to adulthood. We also found that children over 12 years has a significantly associated with seizure outcome and IEDs reduce. A previous study reported that 42% of children exhibited academic underachievement [15], the same rate comparable to our findings (40.2%). Persistent interictal spikes in

EEG may indicate neuropsychological impairment in children with SeLECTS. Research has demonstrated that children with continuous IEDs were at a higher risk of experiencing cognitive deficits [6, 16].

The correlation between SWI and neuropsychological impairment was well-established. Research investigating the impact of IEDs on cognition concludes that IEDs, particularly when highly frequent, could adversely affect cognitive performance in children [4, 17]. A prospective study demonstrated a positive correlation between IEDs on EEG during sleep and increased attention deficit and impulsivity [18]. Frequent IEDs were identified as a potential risk factor for learning and behavioral difficulties. However, one study reported that cognitive deficits were only associated with spike location[19]. Patients with ESES did not appear to undergo cognitive regression over time[20]. Seizure burden and prolonged seizure duration were correlated with cognitive impairment [21]. Conversely, other studies indicated that academic performance in SeLECTS was not significantly correlated with seizure frequency [22].

In this study, we conducted a retrospective analysis of 107 children with SeLECTS to investigate the relationship between SWI, ASM usage, seizure burden, and academic performance. Our findings suggested that while SWI and IEDs patterns was not significantly associated with academic achievement, the number of ASMs and seizure burden before treatment were significant predictors of academic performance. Specifically, children who experienced more seizures (≥ 5) and required multiple ASMs (≥ 2) were more likely to exhibit lower academic achievement scores. This suggested that early initiation of ASM therapy may be crucial in mitigating the cognitive and academic impact of SeLECTS. In this study, the seizure outcome and SWI were not associated with academic achievement. The occurrence of seizures did not appear to be decisive for the presence of cognitive impairments [23].

Multiple studies have demonstrated no significant correlation between the age of epilepsy onset and the presence of neuropsychiatric issues in SeLECTS [24]. However, an earlier investigation [25] proposed that seizure onset prior to eight years of age could serve as a potential indicator for identifying patients at risk of academic challenges. Notably, this study revealed an association between older age at epilepsy onset and a more significant reduction in SWI at final follow-up. This finding suggested that early intervention may not only enhance seizure control but also diminish the burden of IEDs, potentially resulting in improved cognitive outcomes. However, the decision to initiate ASM therapy in children with SeLECTS remains a subject of debate, considering the self-limited nature of the condition and the possibility of spontaneous remission [26]. Clinicians must carefully balance the advantages of early treatment against the potential risks of medication side effects and the possibility of unnecessary treatment in children who may not require long-term therapy [27].

The available evidence supported the hypothesis that there were no significant differences in neuropsychological features between children with SeLECTS who received ASM therapy and those who did not [28]. A recent study demonstrated that ASMs might be utilized to suppress IEDs and enhance cognitive performance, independently of seizure frequency [29]. SeLECTS often has a favorable prognosis, ASM selection and dual therapy should be considered, along with the side effect profile and

cognitive effects of the medicine. Dual therapy was mostly administered to young patients and higher SWI[30]. In our study, 68.2% children were using only one ASM, and seizure control was achieved with monotherapy in 71.3% of the children. The type of ASMs was not a significant predictor of performance on seizure outcome and school achievement.

Several factors can potentially influence academic outcomes. In our multivariate analysis, only the number of seizures before treatment was significantly associated with school achievement. This finding suggests that fewer seizures may indicate a shorter duration of seizure persistence and consequently, less disruption to normal brain function.

Despite these insights, our study presents several limitations. Firstly, the retrospective design and relatively small sample size may restrict the generalizability of our findings. Larger, prospective studies were necessary to further investigate the relationship between SWI, ASM usage, and cognitive outcomes in children with SeLECTS. Moreover, our study did not evaluate other potential confounding factors, such as sleep architecture, parental education levels, or socioeconomic status, which may also affect academic performance. Future research should consider these variables to provide a more comprehensive understanding of the factors influencing cognitive and academic outcomes in children with SeLECTS.

Conclusions

In conclusion, this study emphasizes the significance of early ASM therapy in children with SeLECTS, especially those experiencing more seizures. Although SWI and IEDs patterns did not directly correlate with academic performance, the number of ASMs and seizure burden as significant predictors of academic achievement. These findings highlight the necessity for a tailored treatment, considering both clinical and EEG features to optimize outcomes for children with SeLECTS. Additional research was required to elucidate the underlying mechanisms of cognitive impairment in SeLECTS and to identify biomarker that can inform treatment decisions [31].

Abbreviations

Self-limited Epilepsy with Centrotemporal Spikes (SeLECTS)

Spike Wave Index (SWI) Antiseizure Medicine (ASM)

Electroencephalogram (EEG) International League Against Epilepsy (ILAE)

Benign childhood Epilepsy with Centrotemporal Spikes (BECTS)

Encephalopathy related to Status Epilepticus during slow Sleep (ESES)

Interictal epileptiform discharges (IEDs) Non-rapid Eye Movement (NREM)

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of the Affiliated Children's Hospital of Shandong University (Approval No.: SDFE-IRB/P-2022036). For this retrospective etiological study, the need for informed consent from the children and their guardians was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work is supported by Science and Technology Development Program of Jinan Municipal Health Commission (No.:2022-1-47).

Authors' contributions

Y.H. Chen contributed to the conception and design of the experiment, drafting of the manuscript, and statistical analysis.

Z.B. Fang contributed to data collection, and analysis and interpretation of data.

Q. Fang contributed to data collection, and analysis and interpretation of data.

Z.F. Gao contributed to the conception of the study and critical review of the manuscript.

J.G. Shi contributed to the conception and design of the experiments, interpretation of the data, critical review of the intellectual content of the manuscript, and acquisition of funding.

Acknowledgements

The authors are grateful to the anonymous reviewers and the editor for their constructive comments and suggestions.

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Figures

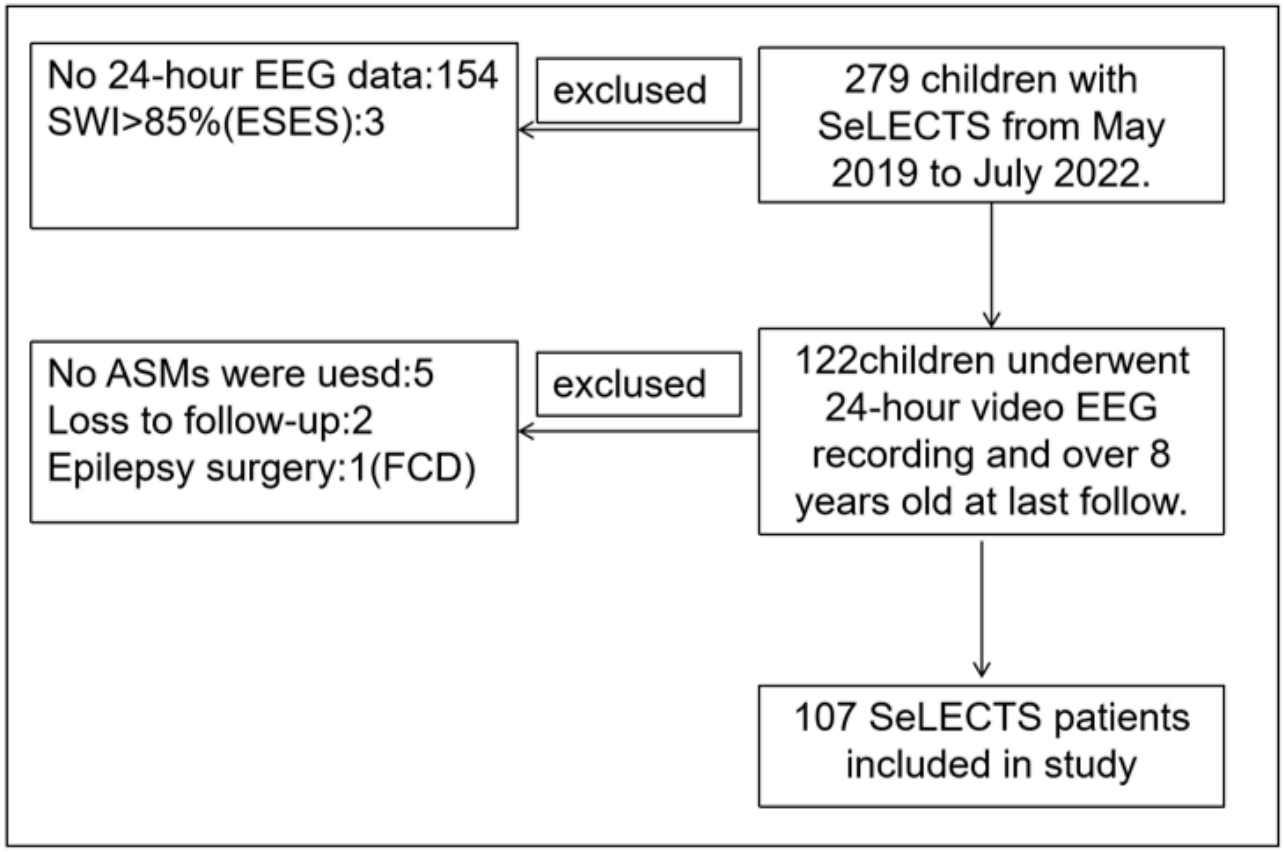


Figure 1

Selection Criteria for SeLECTS Patients. Children with SeLECTS were identified as above.