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To Compare Complex Febrile Seizures and Postictal Electroencephalogram (EEG) With and Without Levetiracetam

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Abstract

Background: Complex febrile seizures (CFS) are seizures that occur more than once in 24 hours or are prolonged (15 minutes) and may be focal. Continuous prophylaxis with anticonvulsants may be considered among children with febrile status epilepticus or frequent CFS. Levetiracetam is one of the newer antiepileptics used in continuous prophylaxis of complex febrile seizures.

Aim: To determine the EEG changes in complex febrile seizures and to evaluate the effect of LEVITRACETAM on EEG in complex febrile seizures.

Methods: This retrospective cohort study included all patients with complex febrile seizures admitted to the tertiary pediatric intensive care unit at Mangalore between January 2017 to May 2024. Children were divided into two groups based on convenience sampling. Group 1 consisted of children who were already loaded with LEVITRACETAM at 40mg/kg after the first CFS. Group 2 included all those who were not on any antiepileptic drug at the time of EEG. EEG findings were analyzed within 48 hours. Based on a previous study conducted by Choudhari PR et al., a sample size of 46 was obtained with a 95% confidence interval and 80% power.

Results: The most common EEG changes noticed in CFS in our study were generalized epileptiform discharges (8.7%), and 36.9 % of the children showed EEG changes. A statistically significant difference was observed (p-value of 0.32) between LEVITRACETAM and EEG. In group 1, 12 children loaded with LEVITRACETAM had abnormal EEG, while in the

group not loaded with antiepileptics, 5 children had abnormal EEG.

Conclusion: EEG abnormalities, particularly generalized epileptiform discharges, were more frequent in children treated with levetiracetam, with a statistically significant association (p = 0.032) between EEG findings and the initiation of therapy. This highlights the utility of EEG in guiding treatment decisions. The study supports levetiracetam as an effective and well-tolerated option for managing CFS in children with EEG abnormalities, emphasizing the need for individualized treatment.

Keywords: Complex febrile seizures, Levitracetam, Electroencephalogram.

Introduction

Seizures that occur in febrile children without any intracranial infection, metabolic disturbance, or history of afebrile seizures between the ages of 6 and 60 months are called febrile seizures.(2) They can be either simple or complex. A simple febrile seizure is characterized by generalized tonic-clonic activity lasting less than 15 minutes, without focal features, and occurring only once within 24 hours or during the same febrile illness. In contrast, a complex febrile seizure involves one or more of the following: focal onset or focal symptoms, a duration exceeding 15 minutes, recurrence within 24 hours, or postictal neurological abnormalities, such as Todd's paresis. (3,4)

Febrile seizures (FS) affect approximately 2% to 5% of children between the ages of 6 months and 5 years, with the highest occurrence around 18 months. They are rare in children younger than 6 months or older than 3 years. The prevalence is notably higher in certain populations, such as 8%–10% in Asians and 5%–10% among Indian children. While males are often reported to experience FS more frequently than females, with a male-to-female ratio ranging from 1.1:1 to 2:1, some large-scale studies have found no significant difference between genders. (5,6) Sometimes in complex febrile seizures, full recovery is not observed after one hour, there are postictal neurological consequences or a short period of paralysis after the seizure (Todd's paralysis), and anticonvulsant drugs may be required to interrupt the seizure. (7) Complex febrile seizure has a higher recurrence rate (8)

The development of febrile seizures is linked to the brain's reaction to elevated body temperature. Fever leads to increased oxygen consumption and heightened basal metabolism, resulting in cellular hyperexcitability due to sodium ion depolarization driven by elevated levels of ATP (Adenosine Triphosphate). Research indicates that mutations in sodium channels may contribute to the persistence of febrile seizures beyond the age of 60 months. (9)

The expert group recommended MRI of the brain with an epilepsy protocol as the preferred neuroimaging technique once the child is stabilized. The primary goal of performing an MRI during the initial episode of a complex febrile seizure is to identify potential causes such as viral encephalitis, acute disseminated encephalomyelitis, virus-related encephalopathy, intracranial space-occupying lesions, cortical malformations, or abnormalities in the hippocampus. (10) For children experiencing their first episode of a complex febrile seizure with prolonged or focal characteristics, an MRI of the brain should be performed within 72 hours. However, routine follow-up imaging is unnecessary if the initial neuroimaging does not reveal an alternative diagnosis. (10)

Routine EEG is not recommended for children with simple febrile seizures. However, it may be considered for those with complex febrile seizures, although its predictive value for future epilepsy remains uncertain. EEG can also be considered in cases where neuroimaging reveals focal abnormalities. When EEG is indicated, it should ideally be conducted within a week of the febrile seizure or as soon as feasible. The EEG protocol should include at least 30 minutes of recording and must capture both sleep and awake states. (10) Though, both pediatricians and specialists recommend EEGs on these children in some countries, in the evaluation of complex febrile seizure, the precise role of EEG is yet to be established. (11)

Research on febrile seizure (FS) management indicates no significant difference in recurrence rates between regular and intermittent use of antipyretic agents. (12) Additionally, antipyretics are not effective in preventing FS recurrence or reducing fever-related episodes leading to recurrent seizures. (13) Current guidelines do not recommend continuous or intermittent use of neuroleptics, such as benzodiazepines, following a simple febrile seizure. (14,15) While antiepileptic drugs (AEDs) like phenobarbital and valproic acid have shown efficacy in preventing FS recurrence, prolonged use is associated with adverse effects, including behavioral changes, irritability, hyperactivity, and reduced cognitive function. (16,17) Intermittent treatment with oral diazepam can lower the risk of recurrent FS, though its effectiveness remains limited. (18)

During the acute phase, management focuses on identifying and addressing the cause of the fever while providing symptomatic relief. Ensuring the child stays hydrated by encouraging fluid intake is essential. Paracetamol or ibuprofen can be used to alleviate discomfort associated with the infection. (19,20) In certain situations, benzodiazepines such as rectal diazepam or buccal/nasal midazolam may be prescribed as rescue medications for use at home to terminate seizures. (21)

Continuous prophylaxis with anti-seizure medications may be considered in specific cases such as febrile status epilepticus, febrile seizures in children with neurodevelopmental delays, frequent complex febrile seizures, or FS+/GEFS+ associated with afebrile seizures. However, it is not recommended for children with simple febrile seizures. Sodium valproate is the preferred medication for continuous prophylaxis, and baseline investigations, such as liver function tests, are not necessary for otherwise healthy children before starting treatment. The duration of therapy typically extends to a two-year seizure-free period or may be tailored based on the underlying condition, such as GEFS+ or Dravet syndrome. Management of febrile status epilepticus should align with standard convulsive status epilepticus protocols, but in children diagnosed with Dravet syndrome or FS+/GEFS+, sodium channel blockers like phenytoin should be avoided. (10)

Levetiracetam is one of the newer antiepileptics used in continuous prophylaxis of complex febrile seizures (7). Levetiracetam (LEV) is a newer antiepileptic drug (AED) that is noted for having fewer potential side effects, particularly in the treatment of brain injury.(22) Studies have demonstrated its effectiveness in preventing the recurrence of febrile seizures. (23) A systematic review and meta-analysis found that LEV is linked to a lower rate of adverse drug reactions and appears to offer similar efficacy to phenytoin in terms of seizure prevention. (24)

In recent years, levetiracetam (LEV) has gained attention as a potential alternative treatment for focal seizures in children. While its exact mechanism of action is not fully understood, it is believed to work by modulating the release of neurotransmitters at synapses. LEV offers several advantages over traditional antiepileptic medications, such as a favorable pharmacokinetic profile, minimal drug interactions, and a lower risk of cognitive side effects. (25) This study aims to correlate the EEGs in complex febrile seizures with and without LEVITRACETAM.

Methods

Primary objective: To determine the EEG changes in complex febrile seizures

Secondary objective: To evaluate the effect of LEVITRACETAM on EEG in complex febrile seizures.

Study design – Retrospective cohort study

Source of data- All children admitted to tertiary care PICU in AJ Institute of Medical Sciences, Mangalore during the study period meeting the Inclusion criteria.

Inclusion criteria: Included patients who had an International Classification of Diseases, Tenth Revision (ICD-10) code for Complex Febrile seizures (R56.01) and EEG obtained after 1st, 2nd or 3rd CFS before maintenance ASM

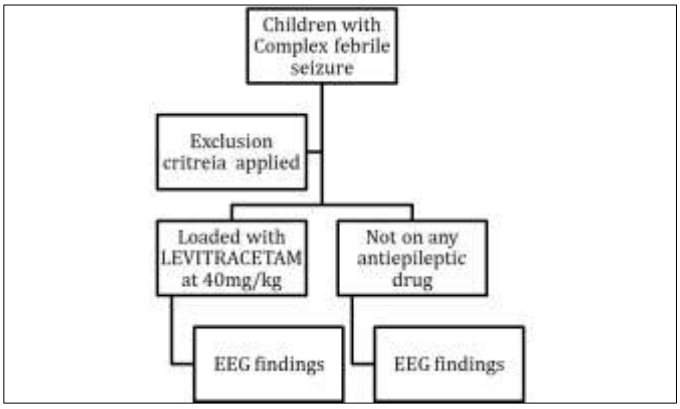
Exclusion criteria

- Simple febrile seizure
- Not undergone EEG study
- Neurodevelopmental delay (including genetic syndromes or brain malformation) or known case of seizure disorder
- Acute symptomatic (e.g. due to CNS infection or ADEM)
- Afebrile seizure preceding the seizure with fever, n = 56

Sampling method: Convenience sampling

Ethical considerations: The research was reviewed and approved by the Institutional Ethics Committee (DCGI Reg. No. EC/NEW/INST/2020/741) dated 24/06/2024). Written informed consent was taken from the patient's parents/ guardian prior to enrolment in the study.

Data Collection: All children who have had complex febrile seizures during the study period will be included. Patient details and EEG findings will be obtained from the medical records department. They will be divided into two groups. Group 1 shall consist of children who were already loaded with loading dose of LEVITRACETAM at 40mg/kg. Group 2 shall include all those who were not on any antiepileptic drug at the time of EEG. EEG findings done within 48 hours will be compared between the two groups.



Sample size: Based on previous study conducted by Choudhari PR et al, proportion of patients prevented from developing seizure in group given the drug was 70% and in the group not given the drug was 60%. Considering the similar proportions in the present study, Sample size can be calculated as follows,

The Sample size is calculated using the formula,

$$n = \frac{(Z_\alpha + Z_{1-b})^2 (p_1 q_1 + p_2 q_2)}{d^2}$$

Where $Z\alpha$ = Standard table value for 95% confidence interval

Z_{1-b}= Standard table value for 80% Power

p_1 = Proportion of patients prevented from developing seizure in group given the drug = 70%

p_2= Proportion of patients prevented from developing seizure in group not given the drug =60%

q= 100-p

d = minimum expected difference between the proportions= 40%

$$n = \frac{(Z\alpha+Z1\text{-}b)^2 (p_1q_1 + p_2q_2)}{d^2}$$

$$n = \frac{(1.96+0.84)^2 (70X30 + 60X40)}{40^2} = \frac{2.8X2.8 (2100+2400)}{1600}$$

n~23

Sample Size: 23 in each group

Total Sample Size: 46

Results

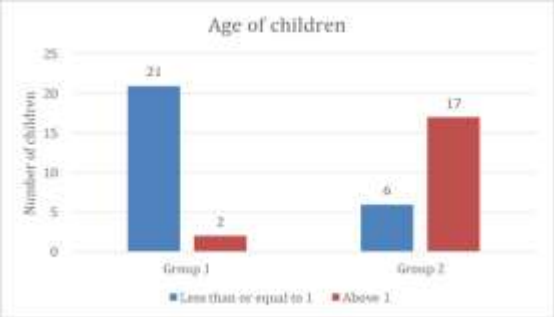
Age distribution

Table 1: Table representing age distribution in both the groups

		Group 1	Group 2
Less than or equal to 1	n	21	6
	%	91.30	26.09
Above 1	n	2	17
	%	8.70	73.91
Total	n	23	23
	%	100	100

In our study, 2 children of the category of children in whom Levitacetam was loaded for complex febrile seizures were above 1 year while the rest were above 1 year. In the other group, 6 children were above 1 year while the rest 17 were less than 1 year.

Graph 1: Graph representing age distribution in both the groups



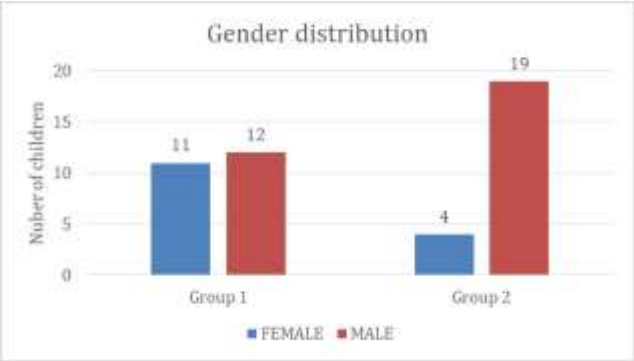
Gender Distribution

Table 2: Table showing gender distribution in the two groups

		Group 1	Group 2
Female	N	11	4
	%	47.83	26.09
Male	N	12	19
	%	52.17	82.61
Total	N	23	23
	%	100	100

In the first group, 11 of the children were females while the rest were males while in the other group 4 of them were males while the rest were females.

Graph 2: Graph showing gender distribution in the two groups



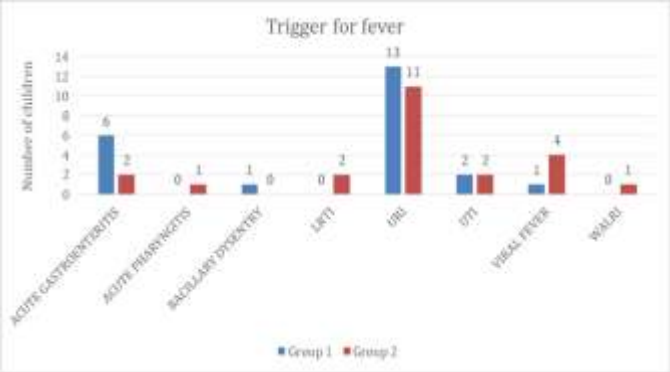
Trigger for fever

Table 3: Table showing the trigger for fever causing complex febrile seizure

		Group 1	Group 2
Acute Gastroenteritis	n	6	2
	%	26	9
Acute Pharyngitis	n	0	1
	%	0	4
Bacillary Dysentry	n	1	0
	%	4	0
LRTI	n	0	2
	%	0	9
URI	n	13	11
	%	57	48
UTI	n	2	2
	%	9	9
Viral Fever	n	1	4
	%	4	17
Walri	n	0	1
	%	0	4
Total	n	9	23
	%	100	100

The causes of fever causing complex febrile seizure in group 1 are acute gastroenteritis (26%), bacillary dysentery (4%), upper respiratory tract infection (57%), urinary tract infection (9%) and viral fever (4%). In the other group causes included acute gastroenteritis (9%), acute pharyngitis (4%), lower respiratory tract infection (9%), upper respiratory tract infection (11%), urinary tract infection (9%), viral fever (17%) and wheeze associated upper respiratory tract infection (4%).

Graph 3: Graph showing the trigger for fever causing complex febrile seizure



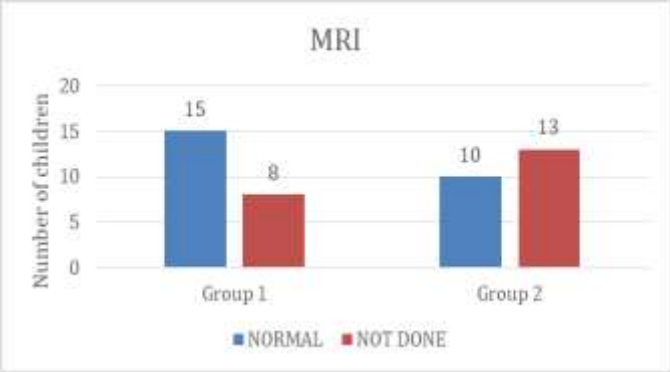
MRI

Table 4: Table showing MRI details

		Group 1	Group 2
Normal	n	15	10
	%	65.22	26.09
Not Done	n	8	13
	%	34.78	56.52
Total	n	23	23
	%	100	100

In the first group, 15 children underwent MRI and were reported normal; in the seco[nd] group, 8 of the children underwent MRI and were reported normal. Ten in the first group and 13 in the second group didn't undergo MRI.

Graph 4: Graph showing MRI details



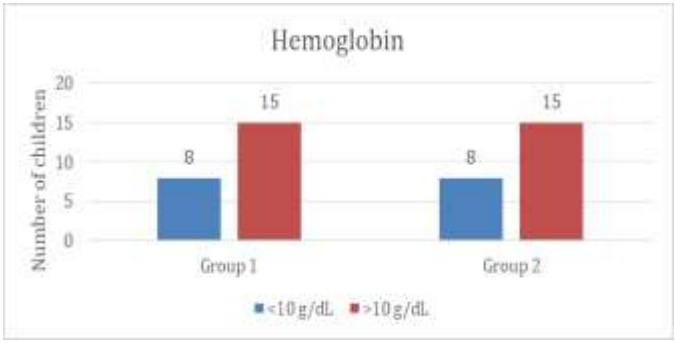
Hemoglobin

Table 5: Comparison of hemoglobin values in both groups

		Group 1	Group 2
<10 g/dL	N	8	8
	%	34.78	26.09
>10 g/dL	N	15	15
	%	65.22	65.22
Total	N	23	23
	%	100	100

Eight children in both the groups had hemoglobin less than 10 g/dl while fifteen children in each group had hemoglobin more than 10 g/dl.

Graph 5: Comparison of hemoglobin values in both groups



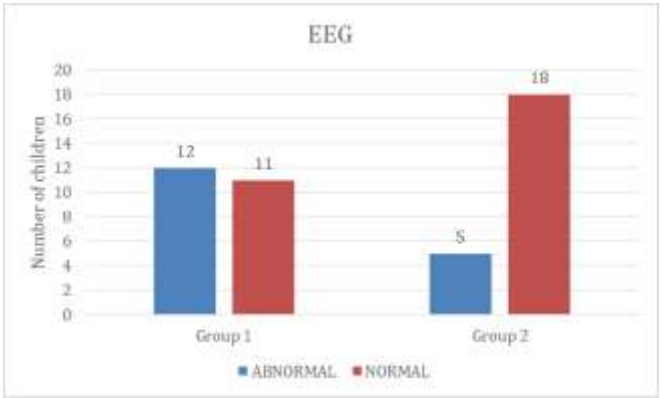
EEG finding

Table 6: EEG findings in two groups

		LEVITRACETAM	Yes	No	Total	Pearson Chi-Square value	Df	p value
EEG finding	Abnormal	Count	12	5	17	4.572[a]	1	0.032
		% within LEVITRACETAM	52.2%	21.7%	37.0%			
	Normal	Count	11	18	29			
		% within LEVITRACETAM	47.8%	78.3%	63.0%			
	Total	Count	23	23	46			
		% within LEVITRACETAM	100.0%	100.0%	100.0%			

Twelve children who had abnormal EEG (52.2%) were started on LEVITRACETAM while 18 children who had no EEG were not loaded with LEVITRACETAM. This shows a p-value of 0.032 which is statistically significant.

Graph 6: EEG findings in two groups



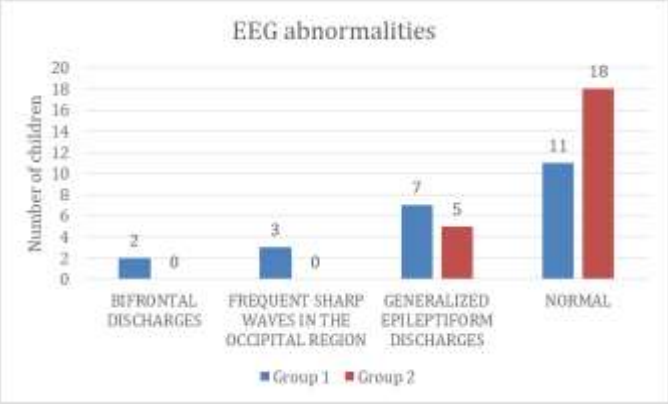
Categorization of EEG discharges

Table 7: Table showing Categorization of EEG discharges

		Group 1	Group 2
Bifrontal Discharges	N	2	0
	%	9	0
Frequent Sharp Waves In The Occipital Region	N	3	0
	%	13	0
Generalized Epileptiform Discharges	N	7	5
	%	30	22
Normal	N	11	18
	%	48	78
Total	N	23	23
	%	100	100

In both groups, the most frequent EEG abnormality observed was generalized epileptiform discharges. In the first group, twelve children exhibited EEG abnormalities, while in the second group, five children had abnormal EEG findings.

Graph 7: Graph showing EEG abnormalities



Discussion

The most common cause of fever leading to complex febrile seizures in the first group was upper respiratory tract infections (57%) while in the second group included viral fever (17%) and upper respiratory tract infections (11%). According to study conducted by Chung B et al, most common infection associated with FS is respiratory tract infection (26) In terms of diagnostics, 15 children in the first group and 8 in the second had normal MRIs. Ten children in the first group and 13 in the second group did not undergo MRI. Hemoglobin levels were less than 10 g/dL in 8 children in both groups, while 15 children in each group had hemoglobin levels above 10 g/dL. EEG abnormalities were seen in 12 children in the first group (52.2%) who were started on levetiracetam, while 18 children without EEG abnormalities were not treated with the drug. This difference had a statistically significant p-value of 0.032. The most common EEG abnormality in both groups was generalized epileptiform discharges, with abnormal EEGs in 12 children in the first group and 5 in the second group. There is a lack of EEG and Complex febrile seizure data and its correlation with LEVITRACETAM. (LEV).

1. Pankaj et al conducted a Cochrane review to assess the use of EEG and its timing after complex febrile seizures in children younger than five years of age and found no RCTs as evidence to support or refute the use of EEG and its timing after complex febrile seizures among children. (27)
2. Purva et al conducted a retrospective cohort study of 621 children with post-CFS EEGs and identified an association between CFS and midline-vertex discharges, which were present in 52% of the 56 EEGs with interictal epileptiform discharges. 4 predictors of future epilepsy were predicted with logistic regression modeling namely: >3 febrile seizures in 24 hours, interictal epileptiform discharges during post-CFS EEG, family history of afebrile seizures, and age of CFS onset ≥ 3 years. (1)
3. Xue-Chao Li et al conducted a prospective study in two groups of children, the no treatment group

(n=51) and the LEV treatment group (n=45) who received oral at a dose of 15-30 mg/kg twice daily at the onset of fever (38˚C) for 1 week (therapy period), followed by a dose increase or decrease every 2 days until complete withdrawal at the beginning of the second week (observation period) which demonstrated that a significant difference (P<0.01) was observed between the two groups in terms of FS recurrence after 50 weeks concluding that LEV is an effective therapeutic agent for the prevention of FS recurrence and reducing the frequency of fever episodes. (28)

4. R. Sownthariya studied the postictal EEG abnormalities of 50 children with febrile seizures and concluded that the most common epileptiform discharge was of Generalized epileptiform activity, and the most common EEG abnormality is slow waves. (29)
5. Hu 2014 et al performed a pilot study on a total of 115 children with seizure onset between 3 months and 5 years (but visiting age from 9 months to 8 years) with a history of 2 or more episodes of febrile seizures, with random assignment of 78 children to the levetiracetam group (receiving orally a dose of 15 to 30 mg/kg/day twice daily for 1 week starting at the fever onset and 37 children to the control group. Among the 19 patients who presented with epileptiform discharge on EEG, 31.58% (6 of 19) had complex FS and 68.42% (13 of 19) had simple FS. 36.84% (7/19) presented generalized spikes and 63.16% (12/19) showed focal spikes. During the 48-week follow-up period, the patients experienced 26 febrile episodes, and none of them presented seizur'e recurrence. Hence they concluded that Intermittent oral LEV can prevent the seizure recurrence of FS accompanied with epileptiform discharge in 48 weeks. (30)

This study has several limitations. First, the sample size was small, which may affect the robustness of the findings. Second, the administration of levetiracetam was based entirely on the discretion of the treating pediatricians, introducing potential variability in treatment decisions. Third, the study was conducted at a single center, limiting the generalizability of the results. Lastly, there was no long-term follow-up to assess neurological development, seizure recurrence, or potential side effects of the medication.

Conclusion

This study underscores the significance of identifying infectious triggers, with upper respiratory tract infections being the most common cause of fever leading to complex febrile seizures (CFS), consistent with prior research. MRI findings were predominantly normal, indicating that routine imaging may be unnecessary unless specific indications are present. Hemoglobin levels did not show a notable correlation with CFS, suggesting anemia is not a significant factor in seizure occurrence. EEG abnormalities, particularly generalized epileptiform discharges, were more frequent in children treated with levetiracetam, with a statistically significant association ($p = 0.032$) between EEG findings and the initiation of therapy. This highlights the utility of EEG in guiding treatment decisions. The study supports levetiracetam as an effective and well-tolerated option for managing CFS in children with EEG abnormalities, emphasizing the need for individualized treatment. These findings highlight key aspects of diagnosis and management, but further multi-centered research is needed to strengthen these conclusions.

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