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THE IMPACT OF AGE ON SEIZURE SEVERITY CHARACTERISTICS IN CHILDREN WITH DRUG RESISTANT EPILEPSY

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ABSTRACT
Drug-resistant epilepsy (DRE) is found in up to one-third of individuals with epilepsy who have received appropriate therapy and this condition causes significant child morbidity and mortality. Epilepsy that appears at an early age is at higher risk of developing DRE. Objective to assess the effect of age on the characteristics of seizure severity in children with DRE. This study used a cross-sectional design involving 36 DRE patients aged 2-18 years at the Child Neurology Polyclinic, Adam Malik Hospital Medan, from September to October 2024. Seizure severity characteristics were assessed using the Global Assessment of the Severity of Epilepsy (GASE) questionnaire instrument. The categorical data are presented in the form of proportions and the effect of age on seizure severity characteristics was analyzed using the chi-square test. There were 36 children with DRE in this study, predominantly aged ≥ 10 years. Bivariate analysis showed a significant effect of age in children with drug resistant epilepsy only on the disruption of activity experienced by children with a p value = 0.036 (p <0.05). Most patients aged ≥ 10 years did not experience activity disorders or experienced mild activity disorders (73.9%), while in patients aged <10 years, most patients experienced severe activity disorders (61.5%). The age of children with drug resistant epilepsy have a significant effect on daily activity disorders.

Keywords: child; drug resistant epilepsy; epilepsy; parent; seizures

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INTRODUCTION

The International League Against Epilepsy (ILAE) has proposed a definition for drug-resistant epilepsy (DRE) in 2010: "failure of optimal clinical trials of two well-tolerated, appropriately selected and used antiepileptic drug regimens (either as monotherapy or in combination) to achieve sustained seizure freedom". Drug-resistant epilepsy in pediatric patients is associated with neuroinflammation and neurodegeneration (Mesraoua et al., 2023; Saing et al., 2024). Seizure severity can be assessed using the classification system issued by the International League Against Epilepsy (ILAE). ILAE provides standards for classifying seizures based on seizure type and severity. Seizure severity is more often assessed based on duration, frequency, and the clinical impact of the seizures on the patient's quality of life, which is associated with an earlier age of onset (Sarmast et al., 2020).

Age can affect the severity of seizures due to several factors, such as nervous system development, underlying medical conditions, and responses to treatment, which can vary by age group. The sensitivity to seizures in children, especially infants and toddlers, is heightened because their nervous systems are still developing (Stafstrom & Carmant, 2015). Variations in seizure types are also observed, with children more likely to experience focal or generalized seizures associated with certain neurological conditions. Early-onset seizures can

be more difficult to control in some cases, particularly if there is a neurodevelopmental or genetic disorder (Moufawad El Achkar et al., 2022).

DRE is estimated to occur in approximately one-third of individuals with epilepsy, but prevalence rates vary depending on the epilepsy syndrome, the cause of the epilepsy, and other factors such as age at first seizure onset and the presence of neurological deficits (Falsaperla et al., 2024; Perucca et al., 2023). DRE is found in approximately 10–20% of all children with epilepsy, and this percentage can increase to 30–40%. DRE has a negative impact on both individuals and society. Patients with DRE are more susceptible to physical and psychiatric complications, and the condition is associated with a higher incidence of sudden death (Lee et al., 2024).

Rapid neuroplasticity in children aged <3 years affects changes in the clinical course of epilepsy (Sukmono et al., 2025). The incidence of DRE is much higher in the first year of life, which accounts for the majority of DRE cases in children and adolescents, as epileptic encephalopathy—characterized by drug-resistant seizures, developmental delays, and intellectual disabilities—mostly occurs during this period (Lee et al., 2024). DRE also limits children's ability to socialize, leading them to experience negative stigma from peers. DRE significantly reduces the quality of life for patients and increases the risk of comorbidities (Zuo et al., 2024). This study was conducted to assess the effect of age on the characteristics of seizure severity in children with DRE.

METHOD

This study is an observational analytical study with a cross-sectional design conducted at the Child Neurology Clinic at Adam Malik Hospital, Medan. Data were collected through direct interviews with parents from September 9 to October 11, 2024. The subjects of the study were DRE patients aged 2-18 years, divided into two age groups: <10 years and >10 years, who met the inclusion and exclusion criteria, using consecutive sampling. All patients and parents were informed about the purpose of this study and signed the informed consent form. This research has been approved by the Health Research Ethics Committee of the University of North Sumatera with No. 1041/KEPK/USU/2024.

The inclusion criteria for this study were DRE patients aged 2–18 years, diagnosed by a neuropediatrician, who were taking monotherapy or combination therapy and had experienced seizures in the past year. The exclusion criteria included patients with false pharmacoresistance, those seizure-free for one year, those receiving non-pharmacologic treatments (such as a ketogenic diet, epilepsy surgery, or vagus nerve stimulation), and those with neurometabolic, neurodegenerative, infectious, or malignant disorders. Seizure severity was assessed using the GASE questionnaire. Review by the ILAE describes the use of GASE, demonstrating its reliability and validity in assessing epilepsy severity. GASE is a single-item measure developed by experts in pediatric neurology, epidemiology, and neuropsychology. It is designed as a clinician's report and can be assessed using either a single or multi-item assessment (Chan et al., 2015).

There are seven aspects of clinical assessment of seizure severity characteristics based on GASE, namely: seizure frequency, seizure intensity or duration, falls or injuries during seizures, number of antiepileptic drugs, effects of antiepileptic drugs, and interference of epilepsy or drugs with daily activities (mild or severe). The GASE assessment score uses a 7-point likert scale that takes into account all aspects of epilepsy. The GASE score assessment is meaningful with the answer choices being 1 = not at all severe, 2 = slightly severe, 3 = somewhat severe, 4 = severe, 5 = moderately severe, 6 = very severe and 7 = extremely severe (Chan et al., 2015).

The data in this study were processed using SPSS version 21. The data are displayed as categorical data in the form of proportions. Assessment of the influence of age on seizure characteristics was carried out by biavariate analysis with chi square or fisher exact test. The results are said to be statistically significant with the p value <0.05.

RESULT

Based on the seizure severity characteristic graph assessed using the GASE questionnaire, there was no significant difference between the seizure severity characteristic variables, except for activity disorders. Among DRE children aged <10 years, 61.5% experienced severe activity disorders, while in children aged ≥10 years, 26.1% experienced severe activity disorders. This is explained in Figure 1.

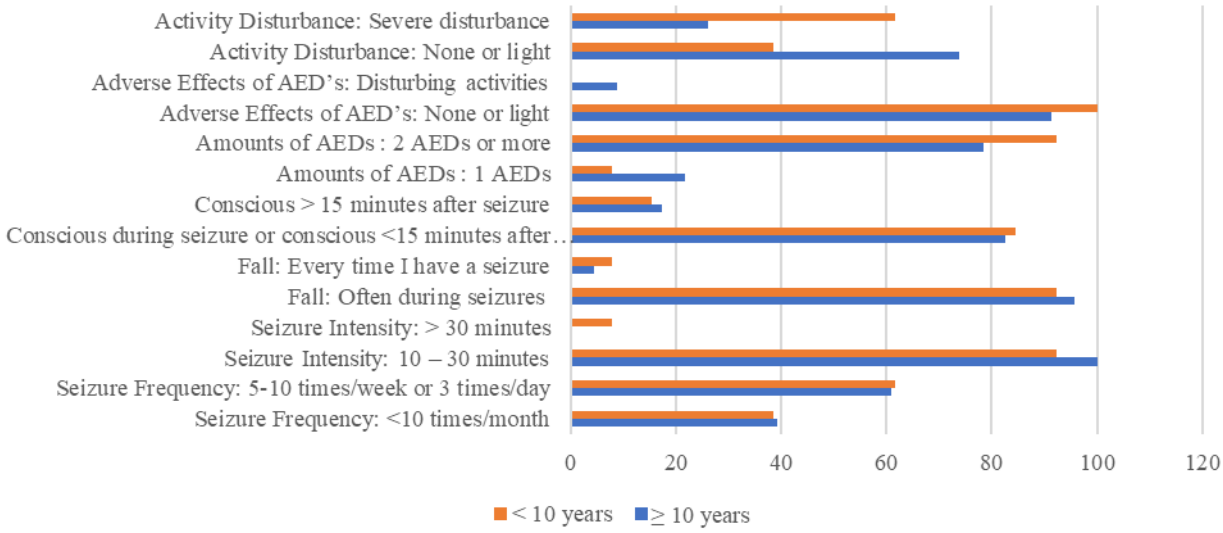

Figure 1. Graph of Seizure Severity Characteristics by Age

Table 1.
Effect of Age on Seizure Severity Characteristics

Demographic Characteristics	< 10 years	≥ 10 years	p (<0.05)
Seizure Frequency, n (%)			
No seizures/<10 x per month	5 (38.5)	9 (39.1)	0.968a
5-10 x/week or 3x/day	8 (61.5)	14 (60.9)	
Seizure Intensity, n (%)			
10 – 30 minutes	12 (92.3)	23 (100)	0.361b
> 30 minutes	1 (7.7)	0	
Fall, n (%)			
Often during seizures	12 (92.3)	22 (95.7)	1,000b
Every time I have a seizure	1 (7.7)	1 (4.3)	
Post Seizure, n (%)			
Conscious during seizure or conscious <15 minutes after seizure	11 (84.6)	19 (82.6)	1,000b
Conscious > 15 minutes after seizure	2 (15.4)	4 (17.4)	
Number of antiepileptic drugs, n (%)			
Singe antiepileptic drug	1 (7.7)	5 (21.7)	0.385b
Two or more antiepileptic drug	12 (92.3)	18 (78.3)	
Side effects of antiepileptic drugs, n (%)			
None/light	13 (100)	21 (91.3)	0.525b
Disturbing activities	0	2 (8.7)	
Activity Disturbance, n (%)			
None/light	5 (38.5)	17 (73.9)	0.036a
Severe disturbance	8 (61.5)	6 (26.1)	

[a]*Chi Square, Fischer's Exact*

To determine the effect of age on the characteristics of seizure severity in children with drug-resistant epilepsy (DRE), a chi-square test and Fisher's exact test were performed according to the criteria. Based on the bivariate analysis, only activity disorders showed a significant association with the age of children with drug-resistant epilepsy, with a p-value of 0.036 ($p < 0.05$). Most patients aged ≥ 10 years did not experience activity disorders or experienced mild activity disorders (73.9%), while most patients aged < 10 years experienced severe activity disorders (61.5%). However, analysis of other patient characteristics, including seizure frequency ($p = 0.968$), seizure intensity ($p = 0.361$), incidence of falls ($p = 1.000$), consciousness after seizures ($p = 1.000$), number of antiepileptic drugs ($p = 0.385$), and side effects of antiepileptic drugs ($p = 0.525$), did not show an association with the age of DRE children.This is explained in table 1.

DISCUSSION

Plants have an extraordinary ability to produce various types of secondary metabolites which are sources of plant-derived antimicrobial substances (PDAms) such as alkaloids, glycosides, terpenoids, saponins, steroids, flavonoids, tannins, quinones and coumarins (Li & Monje-Galvan, 2023). The flavonoids in kersen leaves work by affecting the bacterial cytoplasmic membrane through the release of transduction energy, which inhibits bacterial motility. This process inhibits bacterial activity by interfering with cell function, namely by denatureting proteins on the bacterial cell wall. The chemical content of saponins causes cell lysis by making the bacterial cell membrane more permeable. Flavonoid-protein interactions (enzymes, receptors, transporters, and transcription factors) are fundamental phenomena that govern the beneficial effects of flavonoids. As mentioned in previous studies, one of the most studied pharmacological effects of flavonoids is their antibacterial properties, which have been thoroughly evaluated through various SAR studies to find more potent antibacterial agents as safe natural products. It can be concluded that several structural features of flavonoids may be important for their antibacterial effects, including C5, C7, C3′, and C4′ hydroxylation and geranylation or prenylation at C6. However, the most important aspect of flavonoids is that they must maintain their amphiphilic characteristics to penetrate bacteria to exert potent antibacterial action. Therefore, these important structural features of antibacterial flavonoids, if taken into account while devising new synthetic strategies, may play a significant role in synthesizing better antibacterial drugs to overcome the severe challenges associated with resistant bacteria (Shamsudin et al, 2022).

Saponins cause lysis or rupture of bacterial cells when they come into contact with bacterial cells. The cell wall of bacteria is damaged and its permeability is impaired when tannins bind to polysaccharides. This shift in permeability stops the rate of bacteria, inhibits their growth, and kills the bacteria one by one. Tannins can inhibit the production of nucleic acid components by bacteria and damage cell walls (Raharjo et al., 2024; Fadel et al., 2021). Saponins are typical amphipathic molecules with both hydrophilic and hydrophobic groups; they readily form clusters in water, which may affect the interaction with their targets. Previous studies have simulated the aggregation behavior of glycyrrhizic acid (GA) in water (Zelikman et al, 2015). The results showed that GA readily forms a tightly packed dimer that can rotate around the triterpenoid group, allowing the surrounding water molecules to induce random motion of the saponin sugar group. In contrast, Kim et al. simulated the aggregation behavior of GA in a hydrophobic environment, mimicking the bilayer core condition, the results showed that GA can form dimers or trimers in heptane solvent, but these are unstable and easily formed or dissociated (Kim etal, 2019).

Tannins are found in a variety of plants including many plant foods and are found in beverages such as tea, coffee, and wine. Fruits including persimmons, cranberries,

blackberries, pomegranates, and grapes are major sources of dietary tannins. Tannins play an important role in plant defense mechanisms and protect against predators such as insects and herbivores. Tannins have even been shown to have potential as traditional medicine preparations to treat various diseases including bacterial infections (Farha et al, 2020). Tannins can also denature proteins. Depending on the concentration, the antibacterial activity of the cream ranged from 15 to 23 mm, with 15% producing the best results (21.33 mm). Kersen leaf extract contains active components such as tannins, flavonoids, and saponins. These compounds function as antibacterial by damaging bacterial cell walls, increasing membrane permeability, and denatureting proteins. Ultimately, this inhibits the development and activity of bacteria.

According to the International League Against Epilepsy (ILAE), drug-resistant epilepsy is defined as the failure of an adequate treatment trial of two well-tolerated, appropriately selected, and used antiepileptic drugs, either as monotherapy or combination therapy, to achieve sustained seizure freedom (Kalilani et al., 2018). The incidence of epilepsy is highest during the first year of life and decreases with age. By age 10, the cumulative incidence of epilepsy is approximately 0.66% (Wysham et al., 2015). The incidence of seizures is highest in children under 3 years of age, with the frequency decreasing as the child ages. Febrile seizures are also common, especially in children under 3 years of age (Gogoi, 2019).

The incidence of DRE gradually declined and reached its lowest level in adolescence, as did focal DRE. The incidence of generalized DRE was higher than that of focal DRE at most ages, and the prevalence of generalized DRE was the highest across all ages. The prevalence of focal and unknown DRE continued to increase with age. This suggests that many patients with focal or unknown epilepsy may have ongoing or worsening symptoms despite the lower initial incidence compared to generalized types. The change is likely due to the decreasing incidence of generalized DRE with age and the potential for improvement or death in patients with generalized DRE over time. Several studies have shown that focal seizures are an independent risk factor for AED resistance (Mangunatmadja et al., 2021).

The assessment of seizure severity was first proposed by Cindy et al., who introduced the use of GASE to assess epilepsy severity. A significant correlation was found, with 80.9% of the seven clinical aspects showing strong associations. Several of these items had the strongest correlation, including seizure frequency at 77.5%, followed by impaired activity and seizure intensity or duration. Weak correlations were observed between GASE scores and falls or injuries during seizures, the number of AEDs, and the severity of the post-seizure period. Based on these significant correlations, the researchers used GASE to assess seizure severity in this study (Chan et al., 2015).

Important components of other factors that contribute to drug resistance include the age at seizure onset, gender, duration and etiology of epilepsy, type of initial seizure, presence of febrile seizures or neonatal (febrile) seizures in the patient's history, family history of epilepsy, presence of neurological deficits, frequency of seizures before treatment was initiated, and electroencephalography (EEG) and neuroimaging findings (Knopek et al., 2024).

Several hypothesized mechanisms explain the pathogenesis of DRE, but one factor that has been shown to play a major role is neuroinflammation. Neuroinflammation can trigger and maintain seizures, and may be involved not only in seizure epileptogenesis but also in the development of drug-resistant conditions. It can also sustain ongoing seizures. Recent evidence suggests that IL-1β activation of the neuronal IL-1 receptor induces activation

through phosphorylation of the N-methyl-D-aspartate (NMDA) receptor, inhibits reuptake, and increases glutamate release. Increased glutamatergic transmission is responsible for greater neuronal excitability. Neuroinflammation plays a role in both immunomodulation and immunosuppression (Falsaperla et al., 2024; Saing et al., 2024).

In all cases of DRE with immune or infectious etiology, there is activation of the innate and adaptive immune systems, resulting in an inflammatory response that primarily involves cells in the brain such as glia and neurons, which is the cause of AED-resistant seizures (Falsaperla et al., 2024). Children who experience seizures before the age of 5 years are more likely to develop drug-resistant epilepsy. Based on a systematic review and meta-analysis conducted by Alare in 2024, it was shown that early-onset seizures (OR: 0.685, 95% CI 0.410-0.960) were correlated with drug resistance. Cortical imaging abnormalities were also found to be associated with the development of drug resistance in epilepsy (Alare et al., 2024). Based on Zuo's research (2024), the dominant age group in children with DRE was 3-6 years old with 49 cases, and 36 cases of children with DRE were over 6 years old (Zuo et al., 2024). Based on Matus' research in 2022, DRE occurs more often in children and young adults. This is influenced by psychiatric comorbidities, other factors such as endocrine disorders, neuroinflammatory processes, neurotransmitter disorders, and stress-related mechanisms can contribute to the development of DRE (Murphy et al., 1995).

Nugroho et al. found DRE in 84/137 (54%) patients. Bivariate analysis showed that age at onset <1 year (odds ratio [OR] 2.31, p 0.016), seizure frequency at onset >5 times/day (OR 3.0, p = 0.011), neonatal seizures (OR 3, p = 0.034), presence of neurological deficit (OR 3.1, p = 0.002), and abnormal EEG findings (OR 2.82, p = 0.013) were significantly associated with DRE. Seizure frequency at onset >5 times, neurological deficit, and abnormal EEG findings were associated with the occurrence of drug-resistant epilepsy (Nugroho et al., 2023). Alare et al. found that age at seizure onset (<5 years), particularly in infants (<1 year), predicted the development of DRE. The incidence of DRE is much higher in the first year of life, which accounts for the majority of DRE cases in children and adolescents, as epileptic encephalopathy characterized by drug-resistant seizures, developmental delay, and intellectual disability most often occurs during this time (Lee et al., 2024).

Rapidly occurring neuroplasticity factors in children aged <3 years influence changes in the clinical course of epilepsy. Sukmono et al. showed that the initial risk factors significantly associated with the occurrence of DRE were abnormal EEG results (p=0.001; OR 4.48; 95% CI 1.82-11.03) (Sukmono et al., 2025). The evolution of abnormal EEG findings, with changes in EEG results at least 12 months after therapy, had a more significant effect on AED resistance compared to abnormal initial EEG findings. Factors during therapy significantly associated with the occurrence of DRE included poor seizure frequency evolution (p=0.048; OR 7.1; 95% CI 1.01-49.7) and a poor initial response to therapy (p=0.01; OR 10.92; 95% CI 2.6-45.87). Poor initial response to AED (OR 72.55; 95% CI 7.08-743.85) and symptomatic etiology (OR 84.71; 95% CI 5.18-1359.15) are independent risk factors for drug resistance in children with epilepsy who have an age of onset above five years (Mangunatmadja et al., 2021).

Huang et al.'s research (2014) found that the highest seizure intensity in children was between 1-10 minutes, affecting 58 children, followed by seizures lasting <1 minute in 26 children, 11-30 minutes in 12 children, and the least frequent duration being >30 minutes, affecting 11 children. These findings were influenced by the etiology of the symptoms, the presence of partial seizures, and the number of seizures before diagnosis, with more than 10 seizures before diagnosis indicating more intense seizure activity (Huang et al., 2014).

In children younger than 10 years, seizure duration lasting more than 30 minutes was observed in 47.7% of children in the PICU (Amonkar et al., 2020). Acute symptomatic seizures, which may also occur in children younger than 10 years, had a longer mean duration of 88.6 minutes (Metsäranta et al., 2004). Seizure frequency also affects patients with DRE. Recurrent seizures have been shown to cause neuronal loss and mossy fiber growth in the hippocampus, which can lead to the formation of recurrent excitatory circuits. In addition, a history of status epilepticus has predictive value for drug resistance. Status epilepticus is caused by reduced inhibition and hyperexcitability, and the longer it lasts, the more GABAergic function decreases, while excitatory input continues, contributing to neuronal death (KARAOĞLU et al., 2021).

Based on Radhito's research (2023), children with DRE experience initial seizures up to 5 times per day. This is not consistent with the results of the study, where the highest seizure frequency was 3 times per day. This discrepancy is because pediatric patients are in the DRE development stage, so the frequency of seizures increases (Nugroho et al., 2023). According to the ILAE 2017, drop seizures are focal seizures (KARAOĞLU et al., 2021). Younger children, especially those with conditions such as Lennox-Gastaut syndrome, may experience more falls due to seizure types like flexor spasms, which are reminiscent of infantile spasms. Children aged >10 years may have a higher prevalence of partial seizures, which are less likely to result in falls. However, the risk of falls remains due to the potential for seizures (Murphy et al., 1995).

Nugroho's research (2023) showed that the majority of children received only one type of drug, with 38.7% (53 children out of a total of 137) using a single drug (Nugroho et al., 2023). According to Moseley's research, around 60-70% of children with DRE became seizure-free with the use of two anti-seizure drugs, and seizure freedom decreased with the addition of a third treatment (Murphy et al., 1995). Based on Gencpinar's research (2024), the effectiveness rate of the first drug was found to be 67% in children with focal onset seizures and 66% in those with generalized onset seizures. The efficacy of the first drug was higher (79%) in children with well-defined epilepsy syndromes compared to those without (65%) (Gencpinar et al., 2025).

The number of medications taken may be higher in older children with drug-resistant epilepsy, as they may require polytherapy to achieve seizure control (Gencpinar et al., 2025). In children under 10 years of age, monotherapy is often preferred to minimize drug interactions and side effects, which can be more pronounced in younger children (Oliva et al., 2021). Based on Torres' research (2020), most DRE patients did not experience side effects from antiepileptic drugs (AEDs). However, the number of AEDs used is a significant factor affecting quality of life (Díaz-Torres et al., 2020). According to Driessen's research (2023), side effects occurred in 50.6% of children with drug-resistant epilepsy treated with lacosamide. The most common side effects were drowsiness (18.2% of patients), followed by behavioral changes (15.6%), headache (9.1%), and dizziness (9.1%) (Driessen et al., 2023).

In children around 10 years of age, cognitive and neurological problems are the most common adverse drug reactions (ADRs) associated with anti-epileptic drugs (AEDs). Valproate has been identified as the leading drug causing ADRs, with a significant number of children experiencing side effects, especially when used in combination with other drugs (polytherapy) (Kaushik et al., 2019). Weight gain is a common side effect of valproate, occurring in 53.1% of patients. However, there is no association between weight gain and age, meaning that children under 10 years of age are not particularly more affected than older children. This study shows that the age of children with drug-resistant epilepsy has a significant effect on the

disruption of activities experienced by these children, with a value of $p = 0.036$ ($p < 0.05$). Although patients with drug-resistant epilepsy make up a small proportion of epilepsy patients, this condition causes significant psychosocial and economic burdens (KARAOĞLU et al., 2021).

The management of DRE is a complex process that requires a long-term and individualized approach. Children with DRE may experience potential side effects such as decreased concentration, hyperactivity, drowsiness, pain, and headaches due to long-term exposure. Additionally, a relationship has been found between drug resistance and psychomotor delays and intellectual disabilities. Language, attention, and behavioral disorders also play an important role. DRE also limits children's ability to socialize, leading them to abandon their interests or experience stigma from peers. DRE significantly reduces the quality of life for patients and increases the risk of comorbidities such as intellectual disability or depression. The use of sequential drugs or long-term combination therapy also contributes to liver damage. Patients are at risk of premature death, with a reduced life expectancy of around 2–10 years (Mangunatmadja et al., 2021; Zuo et al., 2024).

CONCLUSION

The age of children with drug-resistant epilepsy has a significant influence on the activity disorders experienced by children but does not show a significant influence on the frequency of seizures, seizure intensity, incidence of falls, the patient's state of consciousness after a seizure, the number of antiepileptic drugs and the side effects of antiepileptic drugs.

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