



Sleep disturbances among 4- to 12-year-old Filipino children with drug resistant epilepsy in a pediatric tertiary hospital

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Objectives: To perform a pilot study on the frequency of sleep-disturbance (Total sleep Disturbance Score (TSD) of > 41) in children diagnosed with Drug Resistant Epilepsy aged 4 to 12 years, using the Children's Sleep Habits Questionnaire (CSHQ).

Methodology: The Children's Sleep Habits Questionnaire (CSHQ) was used to screen for sleep disturbances among 73 patients aged 4 to 12 years old with drug-resistant epilepsy seen at the Seizure Clinic of Philippine Children's Medical Center. Descriptive statistics were used to characterize sociodemographic variables, and sleep and epilepsy-related variables. Continuous data were presented as mean \pm standard deviation (SD), and categorical data as frequencies (percentages).

Results: Sleep disturbances were common and severe in children with drug-resistant epilepsy. Out of the seventy-three participants, 61 patients had a TSD score of greater than 41 (84%) and 12 (16%) had TSD scores below 41 with a mean CSHQ score of 58. The most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%). Meanwhile, the least frequently occurring sleep disturbances involve the domains of sleep disordered breathing (76%), parasomnias (65%), and sleep anxiety (56%).

Conclusion: Majority of the children with drug-resistant epilepsy are sleep disturbed exhibiting high TSD scores (>41) using the Children's Sleep Habits Questionnaire. We recommend to actively evaluate and screen for sleep and behavioral problems concurrently in children with epilepsy.

Keywords: *Epilepsy, Sleep Disturbance, Seizure Recurrence, Pediatrics*

INTRODUCTION

Sleep disturbances – ranging from bedtime resistance and frequent night wakings to obstructive sleep apnea and narcolepsy – affect approximately 25 to 40% of the pediatric population worldwide. ^[1]

Regardless of the type of sleep disturbance, each can have a significant impact on daytime functioning and development – that is learning, growth, behavior, and emotion regulation – of the child, and will most likely persist if left untreated.^[2]

Among the different populations of children, those with epilepsy, developmental disabilities, chronic health conditions, and psychiatric disorders have the most reported cases. Sleep plays a crucial role in modulating seizure occurrence and or interictal epileptiform discharges and at the same time sleep disturbances worsen epileptic symptoms. Hence, epilepsy with the added sleep disturbances exacerbates a child's health and functioning.^[4] In the past years, studies have been conducted to investigate the use of appropriate antiepileptic drugs (AED) to eliminate seizures. However, a fraction of these patients still suffer from seizures despite taking AEDs in adequate doses. The three main categories to consider for the management of refractory epilepsy are: (1) pharmacotherapy, (2) epilepsy surgery and (3) lifestyle changes.^[5] In terms of lifestyle, sleep disturbances in children with drug resistant epilepsy are found to cause increasing seizure frequency. Screening for factors such as sleep disturbance that may be contributory to the recurrence of seizures despite being adequately treated with anti-epileptic drugs can help in finding a more holistic approach in managing patients with drug resistant epilepsy.

One of the lifestyle factors that contribute to the intractability of seizures include the sleeping habits of children with epilepsy. In young children, virtually all problems including bedtime problems and night waking are defined by their caregivers

and its definition is influenced by a host of variables such as parent education level, parental psychopathology, family dynamics, household composition, and parenting styles. The definition of these sleep disturbances may also be developmentally based, namely transient problems that can be understood in the context of normal physical, cognitive, and emotional changes occurring at various developmental stages.^[3] However, there has been an effort to categorize sleep disturbances into 8 domains, as suggested by Owens, Spirito, and McGuinn^[1] in their development of the Children's Sleep Habits Questionnaire (CSHQ). The eight domains are the (1) bedtime resistance, (2) sleep onset delay, (3) sleep duration, (4) sleep anxiety, (5) night waking, (6) parasomnias, (7) sleep disordered breathing, (8) daytime sleepiness. A study on the relationship between Sleep disturbances and behavioral problems in children with epilepsy using the CSHQ showed that higher seizure frequency was related to higher scores for excessive sleepiness.^[4] Children on polytherapy presented with worse sleep problems than children on monotherapy. Findings on previous studies that used the CSHQ showed that children with epilepsy with sleep disturbances presented with higher emotional symptoms, conduct problems, hyperactivity/attention, and peer relationship problems than those without.

The Children's Sleep Habits Questionnaire (CSHQ) is a parent-report

screening tool designed for school-aged children (4-12 years). In the Philippines, the validated Filipino version created by Mabilangan and Moral-Valencia^[6] have been used in 3 local studies that utilized the tool in screening for sleep disturbances in various populations – Autism Spectrum Disorder, Asthmatic Children, and School-aged Children. While the CSHQ has already been used in screening for sleep disturbances in children with drug resistant epilepsy in other Asian countries, there is no available local study yet that used this tool in this specific population in the Philippines. This pilot study aims to determine the frequency of sleep-disturbance (TSD score of > 41) in children diagnosed with Drug Resistant Epilepsy, consulting at the outpatient department of the Philippine Children's Medical Center, using the CSHQ. Also, this study intends to describe the demographic characteristics of children with Drug Resistant Epilepsy (Age and Gender), describe the seizure medications, seizure frequency, seizure pattern, and seizure duration in sleep disturbed children with Drug Resistant Epilepsy. Findings of this study can be used as baseline data for further studies such as, but not limited to, validation and modification of the CSHQ for children with drug resistant epilepsy. Creation of a screening tool for this specific population can help clinicians in recognizing sleep disturbances. Addressing sleep problems in this specific population can lead to better seizure control.

METHODOLOGY

The present research is a cross-sectional study using a self-administered questionnaire to be completed by the parents and/or caregivers of children with: (1) drug-resistant epilepsy who are on two or more antiepileptic drugs and, (2) Aged 4 to 12 years old. Children with drug-resistant epilepsy must have previously received a clinical diagnosis of drug-resistant epilepsy from a neurologist and are currently being seen at the outpatient department of Philippine Children's Medical Center.

The study excluded the following: (1) children taking other medications that are not anti-epileptic drugs that may have an effect on sleep such as psychostimulants (methylphenidate), atypical antipsychotics (risperidone), and antihistamines (diphenhydramine)^[4] (2) children with intake of stimulants such as but not limited to caffeine and nicotine.

The Children's Sleep Habits Questionnaire (CSHQ) is a parent-report screening tool designed for school-aged children (4-12 years). It was developed by by Owens, Spirito, and McGuinn^[1] while the validated Filipino version was created by Mabilangan and Moral-Valencia.^[6] The CSHQ is comprised of 33 items representing eight sleep disturbance subscales: 1) bedtime resistance, 2) sleep onset delay, 3) sleep duration, 4) sleep anxiety, 5) night wakings, 6) parasomnias, 7) sleep-disordered breathing, and 8) daytime sleepiness.^[1]

^[1] The parents are asked to recall their child's sleep habits in a recent typical week. Items are rated on a 3-point Likert scale (rarely = 0-1 night per week; sometimes = 2-4 nights per week; usually = 5-7 nights per week) and each item is evaluated if the sleep behavior represented a problem or not.

The total sleep disturbance score is equivalent to the sum of all 33 subscale items. The cut-off score is 41 with 0.80 sensitivity and 0.72 specificity, implying this score correctly identifies 80% of the clinical sample.^[1]

In addition to the above assessment, parents also reported patient characteristics including age, sex, and their children's seizure history.

The sample size was computed using the sample size for frequency in a population formula via the Epi_info/STATCALC EXE online software. With a confidence interval of 90%, a minimum of 72 patients should be included in this study.

DATA ANALYSIS

Descriptive statistics were used to characterize sociodemographic variables, and sleep and epilepsy-related variables. Continuous data were presented as mean \pm standard deviation (SD), and categorical data as frequencies (percentages).

RESULTS

Seventy-three (73) parents from the out-patient department of Philippine

Children's Medical Center were surveyed to assess the sleep habits of their children with drug resistant epilepsy (4-12 years old). Findings from this research indicate that sleep disturbances were more prevalent among male children, with an average age of 7.42 years old.

Table 1 below shows the frequencies of how many parents rated each sleep habit or item as occurring usually (5 to 7 times in a week), sometimes (2 to 4 times), and rarely (0 to 1 time). The most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%).

In the domain of bedtime resistance, the most frequently occurring sleep habits were: falls asleep in other's bed (51%), needs a parent in the room before being able to sleep (44%), and afraid of sleeping alone (41%). Sleep onset delay was reported in 19% of children with drug resistant epilepsy and 16% of the parents reported that their children sleep too little. In terms of night wakings, 44% of the parents reported that their children usually wake up once during the night while 38% reported that their children usually wakes up more than once per night. Meanwhile, the most commonly occurring sleep disturbance under the domain of daytime sleepiness were: children looking tired the whole day (36%), children having a hard time getting out of bed (32%), and falling asleep while watching the television (30%).

Table 1. Frequencies and Percentages of the Sleep Habit of Children with Drug Resistant Epilepsy

DOMAIN	Usually	Sometimes	Rarely
	%	%	%
BEDTIME RESISTANCE			
SLEEP ONSET DELAY	29%	21%	50%
SLEEP DURATION	19%	53%	27%
SLEEP ANXIETY	14%	26%	50%
NIGHT WAKINGS	22%	23%	56%
PARASOMNIAS	28%	26%	47%
SLEEP DISORDERED BREATHING	11%	24%	65%
DAYTIME SLEEPINESS	6%	18%	76%
TOTAL	23%	36%	41%
	19%	30%	51%

Note: Percentages may not total to 100% due to rounding

On the other hand, the least frequently occurring sleep disturbances involve the domains of sleep disordered breathing (76%), parasomnias (65%), and sleep anxiety (56%). Only 18% of the parents reported that their children usually snore loudly at night. Meanwhile, 92% of the respondents reported that their children rarely experience gasping and stopping of breathing during their sleep. In terms of anxiety, respondents reported that 44% of their children needs a parent in the room before being able to sleep and 41% are afraid to sleep alone. On the other hand, 58% of the parents reported that their children rarely get afraid of sleeping in the dark.

In terms of TSD scores, a TSD score of greater than 41 is the cut-off for determining sleep disturbed children. Table 2 summarizes the demographic characteristics of children with drug resistant epilepsy. Based on the table, out of the seventy-three participants, 61 patients had a TSD score of greater than 41 (84); on the other hand, only 12 (16%) had TSD scores 41 or lower. The average age of children TSD scores greater than 41 is 7.62 ± 2.23 while there is a lower average age of 6.42 ± 1.78 in those children who scored lower than 41. Meanwhile, both groups differ by only 3% in terms of the average age at seizure onset. Sleep disturbance is also found to be more common in males (63%) than in females (37%).

Table 2. Demographic Characteristics of Sleep Disturbed (CHSQ>41) Children with Epilepsy compared to Non-Sleep Disturbed (CHSQ <41) Children with Epilepsy

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Age, years	7.42 ± 2.19	7.62 ± 2.23	6.42 ± 1.78
Age at seizure onset, years	3.89 ± 1.25	3.9 ± 1.33	3.8 ± 0.83
Duration of epilepsy, months	42.41 ± 21.73	44.66 ± 20.57	31.05 ± 24.78
Gender			
Male	45 (61%)	39 (63%)	6 (50%)
Female	28 (39%)	22 (37%)	6 (50%)

Note: Data are presented as mean ± standard deviation (SD) or n (%)

As shown in Table 3, those who are sleep disturbed have a shorter average sleeping time of 8.11 ± 1.98 as compared to the non-sleep disturbed group with an average sleeping time of 10.72 ± 1.60 .

Table 3. Average Sleep time of Children with Drug Resistant Epilepsy

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Total sleep time per 24h (hours)	8.42 ± 2.04	8.11 ± 1.98	10.72 ± 1.60

Table 4 shows the distribution of patients according to seizure frequency in the last 6 months. Majority of the patients (56%) had monthly seizure recurrence. 32 (52%) of the 61 patients with TSD scores higher than 41 experienced monthly seizures; while only 10 (83%) of the 12 patients with TSD scores lower than 41 experienced monthly seizure recurrence.

The three (4%) patients who were reported to have daily seizure episodes had TSD scores greater than 41. Majority of the patients in the sleep disturbed group had weekly (34%) and monthly (52%) seizure recurrences; while in the other group, majority of the patients had monthly (83%) or less than 1 seizure episode per month (17%).

Table 4. *Distribution of Patients According to Seizure Frequency in the last 6 months*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Seizure frequency in the last 6 months			
Daily	3 (4%)	3 (5%)	0 (0%)
Weekly	22 (30%)	21 (34%)	1 (8%)
Monthly	41 (56%)	32 (52%)	10 (83%)
Less than 1 per month	7 (10%)	5 (8%)	2 (17%)

Figure 1 shows that higher TSD scores were observed in patients with higher seizure frequency, with those having once a month seizure averaging a score of 43.29 on the CSHQ and those with daily seizures averaging a score of 57.33.

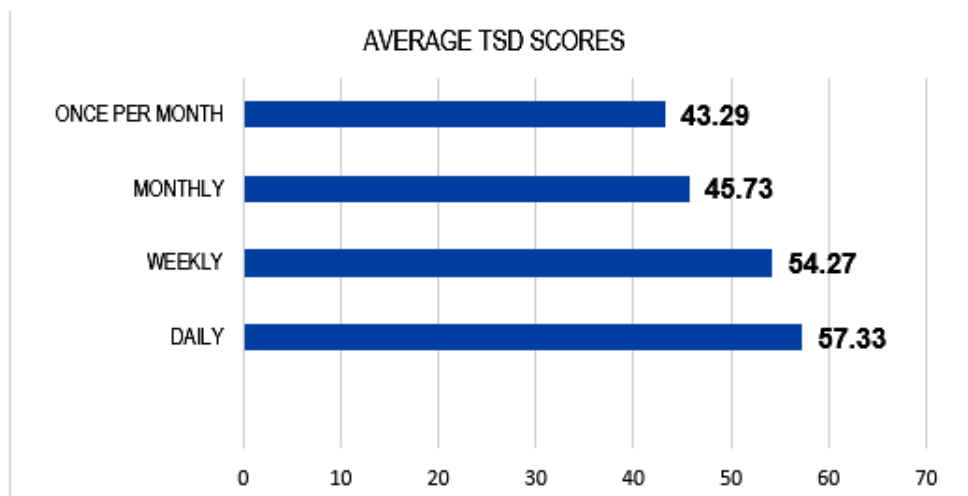


Figure 1. *Seizure frequency and Average TSD Scores of Children with Drug Resistant Epilepsy*

As shown in Table 5, majority of the patients had focal epilepsy (82%), while only 18% had generalized epilepsy. Regarding diurnal patterns, 52 patients (71%) experienced seizures during the daytime, while 12 patients (16%) had more frequent seizures at night. Among the patients with significant TSD scores, 50 (82%) had focal epilepsy, and 46 patients (75%) experienced

seizure episodes during the day. Concerning seizure duration, 57 patients (78%) reported seizure episodes lasting for 5 minutes. Additionally, 13 patients (18%) out of 73 experienced seizure episodes lasting from 5 to 15 minutes, while 3 patients (4%) reported seizures lasting from 16 to 30 minutes, resulting in hospitalization in the past 6 months.

Table 5. *Distribution of Patients According to Seizure Type, Pattern, and Duration*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Seizure Type			
<i>Focal</i>	60 (82%)	50 (82%)	10 (83%)
<i>Generalized</i>	13 (18%)	11 (18%)	2 (17%)
<i>Unclassified</i>	0 (0%)	0 (0%)	0 (0%)
Seizure Diurnal Pattern			
<i>Day</i>	52 (71%)	46 (75%)	4 (34%)
<i>Night</i>	12 (16%)	8 (13%)	2 (16%)
<i>Both</i>	9 (12%)	7 (12%)	6 (50%)
Seizure Duration (min) in the last 6 months			
< 5	57 (78%)	48 (79%)	9 (75%)
5-15	13 (18%)	10 (16%)	3 (25%)
16-30	3 (4%)	3 (5%)	0 (0%)
>30	0 (0%)	0 (0%)	0 (0%)

Table 6 shows the breakdown of patients according to their anti-epileptic medications. The most frequently prescribed drug among the patients in this study is Levetiracetam, utilized by 93% of them. Following closely are Phenobarbital (46%) and Oxcarbazepine (39%). Conversely, Valproic acid (36%) and Topiramate (32%) were less commonly prescribed. Interestingly, these medication trends were consistent across both groups.

Table 6. *Distribution of Patients According to Anti-Epileptic Medications*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
<i>Levetiracetam</i>	68 (93%)	57 (93%)	12 (100%)
<i>Phenobarbital</i>	34 (46%)	30 (49%)	4 (33%)
<i>Oxcarbazepine</i>	29 (39%)	25 (40%)	4 (33%)
<i>Topiramate</i>	24 (32%)	24 (39%)	1 (8%)
<i>Valproic acid</i>	26 (36%)	24 (39%)	2 (17%)

DISCUSSION

Sleep disturbances are among the most prevalent comorbidities of epilepsy, with prevalence ranging 45–95% among children with epilepsy, as compared with 25–40% among typically developing children. The current study showed that sleep disturbances were common and severe in children with drug resistant epilepsy, with a frequency of 84% and a mean CSHQ total score of 58. In China, CSHQ total score of was 45.92 from a sample of children with epilepsy aged 4 to 12 years old with prevalence of 73.7%. A study among Hong Kong children with epilepsy aged 4 to 12 years old CSHQ total and a study among American children with epilepsy aged 2 to 10 years reported a CSHQ total score of 48.25.^[4]

The average age of children TSD scores greater than 41 is 7.62 ± 2.23 while there is a lower average age of 6.42 ± 1.78 in those children who scored lower than 41. Meanwhile, both groups differ by only 3% in terms of the average age at seizure onset. Sleep disturbance is also found to be more common in males (63%) than in females (37%). Men are generally more prone to excitability episodes and epileptic seizures than women. While the exact molecular mechanisms behind this difference are not fully understood, variations in the brain's structure and neural pathways between men and women may help explain why men are more vulnerable to seizures and epileptic events. Changes in sensitivity to seizures can

be attributed to steroid hormones, including fluctuations in neurosteroids and alterations in how their receptors signal.^[8]

Sleep Habits in Children with Epilepsy

One of the identified lifestyle factors that contribute to the intractability of seizures include the sleeping habits of children with epilepsy. A study on the relationship between Sleep disturbances and behavioral problems in children with epilepsy showed that higher seizure frequency was related to higher scores for excessive sleepiness.^[4] Data gathered from this study showed that higher seizure frequency is seen in patients with higher TSD scores as previously described in Figure 1. There were 3 patients who was reported to have daily seizures and their average TSD score is 57.33. This is 20% higher than the average TSD score of those patients with monthly seizure recurrence (Average score: 45.73). Sleep plays a crucial role in modulating seizure occurrence and or interictal epileptiform discharges and at the same time sleep disturbances worsen epileptic symptoms. Sleep and epilepsy has a bidirectional relationship where in epileptic discharges have also been shown to disrupt sleep-wake cycles. Children with poorly controlled seizures had even worse sleep habits compared with children with better control of seizures. Hence, epilepsy with the added sleep disturbances exacerbates a child's health and functioning.^[4]

The interaction between sleep and epilepsy is complex with children with epilepsy having poorer sleep with clinically defined sleep disorders than their healthy counterparts.^[5] In another study, it was found that the most common sleep disturbances in children with epilepsy include excessive daytime sleepiness (76%), sleep disordered breathing (65%), and parasomnia (53%).^[4] Data gathered from this study showed that the most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%). On the contrary, disordered breathing (76%), parasomnias (65%), along with sleep anxiety (56%) were found to be the least frequently occurring sleep disturbances among the studied participants. Obstructive Sleep Apnea is the most common form of sleep-disordered breathing. Although this condition is highly prevalent in children with epilepsy, it is usually an underrecognized and underdiagnosed condition due to lack of parental awareness. unrecognized by the parents due to lack and is highly prevalent and grossly underdiagnosed.^[9] Only 18% of the parents reported that their children usually snore loudly at night. Meanwhile, 92% of the respondents reported that their children rarely experience gasping and stopping of breathing during their sleep.

Results of this study showed that in the domain of bedtime resistance, the most frequently occurring sleep habits were: falls

asleep in other's bed (51%), needs a parent in the room before being able to sleep (44%), and afraid of sleeping alone (41%). Sleep onset delay was reported in 19% of children with drug resistant epilepsy and 16% of the parents reported that their children would sleep too little. In terms of night wakings, 44% of the parents reported that their children usually wake up once during the night while 38% reported that their children usually wakes up more than once per night. Meanwhile, the most commonly occurring sleep disturbance under the domain of daytime sleepiness were: children looking tired the whole day (36%), children having a hard time getting out of bed (32%), and falling asleep while watching the television (30%). This coincides with the findings in another study that lack of a bedtime routine, having irregular bedtimes and risetimes, and frequent daytime napping are among the most common sleep problems identified in this specific population.^[10]

Sleep duration

In terms of sleep duration, results show that patients with significantly higher TSD scores have a shorter average sleeping time of 8.11 ± 1.98 as compared to the non-sleep disturbed group with an average sleeping time of 10.72 ± 1.60 . Children aged 3 to 5 years of age should sleep 10 to 13 hours per 24 hours (including naps) on a regular basis to promote optimal health while children 6 to 12 years of age should sleep 9 to 12 hours per 24 hours.^[11]

Given this data, it can be said that majority of the children with significantly higher TSD scores are not getting the appropriate length of sleep that is recommended for their age and this may contribute further to seizure recurrence. Majority participants with low TSD scores (<41) reach the optimal length of sleep per age and thus the data also showed a lower seizure recurrence rate and shorter seizure duration wherein only 8% of the patients have weekly seizure episodes compared to the 34% of the participants with significant TSD scores. A case-control study conducted in Hong Kong reported that 50 minutes less sleep during weekdays compared with weekends in 63 epileptic preschool- and school-aged children led to increasing seizure recurrence.^[12]

Effects of Anti-Epileptic Medications

It is important to consider how antiepileptic medications can impact sleep. Results of this study showed that the most common drug used by 98% of all the patients surveyed is Levetiracetam. This was followed by Phenobarbital (46%) and Oxcarbazepine (39%). The least commonly used drugs include Valproic acid (36%) and Topiramate (32%). All of the patients included in this study are taking multiple antiepileptic medications (polytherapy) and among those patients with significantly higher TSD scores, the most commonly used AED used include: Levetiracetam (93%), Phenobarbital (49%), and Oxcarbazepine (40%). Only 4 patients (33%) use Phenobarbital among those patients

with low TSD scores. Benzodiazepines and barbiturates are known to affect sleep by reducing the time it takes to fall asleep, valproate increases the duration of the first stage of sleep, and Lamotrigine reduces slow wave sleep, which can lead to insomnia.^[4] Moreover, children who are on multiple antiepileptic medications (polytherapy) tend to experience more sleep-related issues compared to those on a single medication (monotherapy). Data gathered from this study showed that sleep onset delay was seen in 19% of children with drug resistant epilepsy. `

Our study's strength lies in the use of validated tools that cover a broad spectrum of relevant factors. However, it's essential to interpret our findings cautiously considering the following limitations: (1) Our sample was drawn exclusively from a single site and the generalizability of our findings may be limited. Future research should aim to replicate and extend our results by involving larger samples from multiple locations; (2) The study did not utilize objective sleep assessments, such as actigraphy or polysomnography, potentially introducing reporting bias. Nonetheless, the Child Sleep Habits Questionnaire (CSHQ) is a well-established tool for screening sleep issues in children with neurodevelopmental disorders and offers measurements that reasonably align with objective data. The study could benefit from clinical evaluations of sleep disorders, psychopathology, and neurodevelopmental

disorders by experienced psychiatrists or developmental and behavioral pediatricians; (3) Due to the cross-sectional design of our study, we cannot establish causal relationships. Longitudinal studies and intervention research can be utilized to comprehensively explore the connections among sleep disturbances and seizure recurrence among children with drug-resistant epilepsy.

CONCLUSION AND RECOMMENDATION

In conclusion, the findings of this study align with previous research indicating that majority of the children with drug resistant epilepsy are sleep disturbed exhibiting high TSD scores (>41) when examined using the Children's Sleep Habits Questionnaire. The CSHQ is a parent-report screening tool designed for school-aged children (4-12 years). The current study showed that sleep disturbances were common and severe in children with drug resistant epilepsy, with a frequency of 84% and a mean CSHQ total score of 58. Sleep disturbances in children with drug resistant epilepsy is found to cause increasing seizure frequency hence screening for factors such as sleep that may be contributory to the recurrence of seizures despite being adequately treated with anti-epileptic drugs can help in finding a more holistic approach in managing patients with drug resistant epilepsy. Furthermore, children with epilepsy with sleep disturbances demonstrated more behavioral problems and lower quality of life compared to those without sleep disturbances. Findings of this study

recommends the need to actively evaluate and screen for sleep and behavioral problems concurrently when seeing children with epilepsy.

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