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Daytime sleepiness in epilepsy patients with special attention to traffic accidents

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ABSTRACT

Purpose: The present study examined clinical variables related to excessive daytime sleepiness (EDS) and sleep disorders in patients with epilepsy (PWE), with special focus on antiepileptic drugs (AEDs), to determine whether sleep-related problems in PWE are correlated with their involvement in traffic accidents.
Method: 325 PWE completed the Epworth Sleepiness Scale (ESS) and 322 the Pittsburgh Sleep Quality Index (PSQI). 239 PWE with a valid driver's license were requested to answer questions related to traffic accidents.
Results: The presence of focal seizures with impaired awareness, age, and administration of lacosamide were each shown to have a significant impact on ESS score. Furthermore, administrations of valproate and lacosamide, as well as sleep-promoting agents other than AEDs (SPA) had a significant impact on the presence of sleep disorder diagnosed with the PQSI. In view of traffic accidents in total, age and LEV had an impact on traffic accident occurrence. In view of an accident in association with an epileptic seizure, SPA was the only variable with a significant impact. As for a traffic accident not related to epileptic seizure, no factors were found to have a significant impact on that dependent variable. No correlation was found between ESS score and any of those 3 traffic accident groupings, which was also true for PSQI.
Conclusions: Neither daytime sleepiness nor sleep disorder was found to be correlated with traffic accidents by PWE who drove. Furthermore, no AED was shown to be correlated with daytime sleepiness or increased risk of a traffic accident.

1. Purpose

Daytime sleepiness in patients with epilepsy (PWE) has been intensively studied, though it remains highly controversial which clinical variable has the greatest relationship. One of the earliest studies of daytime sleepiness in PWE conducted by Hoeppner et al. [1] emphasized the role of epileptic activity in enhancing daytime sleepiness. While some ensuing reports supported that view [2], others did not and instead of epilepsy-related influence proposed other factors. Along with psychiatric co-morbidity and sleep disorders such as restless leg syndrome, antiepileptic drugs (AEDs) have also been reported to potentially cause excessive daytime sleepiness (EDS) in PWE [2]. In Japan, medical package inserts, official documents approved by the Pharmaceuticals and Medical Devices Agency (PMDA), prohibit PWE who take AEDs to drive a motor vehicle, though that is contradictory to the Road Traffic Act in Japan, which allows PWE without a seizure for 2 years to drive regardless of medication. However, no prospective studies regarding EDS in PWE in Japan have been conducted. In the present study, we attempted to confirm clinical variables possibly related to EDS and sleep disorders in PWE with special interest in AEDs, and also examined whether sleep-related problems are correlated with traffic accidents in these patients.

2. Methods

All patients aged 18 years or older who visited the Epilepsy Center of Aichi Medical University or Suzukake clinic from June 2016 to March 2018 and were taking AEDs regularly because of epilepsy were invited to participate in this study. Those with co-morbid intellectual disability, alcohol abuse, severe psychiatric illness, or dementia were excluded. Following approval from the Ethical Committee of Aichi Medical University (2016-H089), the patients were examined with the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). In addition, they were requested to answer questions related to traffic accidents, possession of a valid driving license, prior history of traffic accidents while driving, and any direct causal relationship of a traffic accident with an epileptic seizure. Only traffic accidents which occurred in the midst of or followed immediately after seizures were

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Table 1
Subjects(n = 325).

Age, years	37.84 (14.65)
Age at epilepsy onset, years	20.63 (14.83)
Gender, female/male	143/182
Epilepsy type, focal	254
generalized	58
others	13
Seizure type, FSWIA	60
bilateral or generalized TC	55
others	38
Number of seizures*, FSWIA	10.46 (134.18)
bilateral or generalized TC	2.13 (16.68)
others	10.81 (68.65)
Number of concomitant AEDs	1.86 (0.45)
Concomitant sleep-promoting drug, Yes	42

Values in parentheses indicate SD.
*Number of seizures within 6 months prior to examination.
FSWIA: focal seizures with impaired awareness; TC: tonic clonic seizures.

regarded to have direct causal relationship with a traffic accident. The ESS, a subjective rating scale developed in 1991 by Johns for assessing sleepiness during daytime, consists of 8 questions, with a total score ranging from 0 to 24 points and a score of 11 points or more indicating the presence of EDS. The PSQI was designed for examining sleep quality and consists of 18 questions recapitulated into 7 categories, such as hours of sleep, sleep latency, and use of sleep medication. The total score ranges from 0 to 21 points and patients with a score of 6 points or more are judged to have a sleep disorder. All patients enrolled in the present study provided written informed consent based on the approval of the ethical committee. Three hundred twenty-five PWE completed the ESS and 322 completed the PSQI.

Age at the time of the examination, age at epilepsy onset, gender, epilepsy type (focal, generalized, others), seizure type [focal seizures with impaired awareness (FSWIA), bilateral or generalized tonic-clonic, others], and number of seizures within 6 months prior to the examination were selected as relevant clinical variables (Table 1). Epilepsy and seizure types were classified based on the ILAE classification proposed in 2017. In the present analysis, focal seizures with dominantly convulsive components as well as hyperkinetic elements were excluded from FSWIA. In addition to those clinical variables, any individual AED being administered at the time of the examination was also included in the analysis (Table 2). The total number of concomitant AEDs and regular intake of potentially sleep-promoting agents (SPAs) other than AEDs, including antipsychotics, antidepressants, and sleep medication, as well as anti-histaminic, anti-anxiety, and anti-dementia agents were also checked. Using total scores of the ESS, multiple regression analysis was performed. Based on the presence or absence of a sleep disorder based on PSQI score as a dependent variable, logistic regression analysis was also performed. Additionally, logistic regression analysis of patients with a driver's license was performed with traffic accident as a dependent variable (n = 239). Among the clinical variables and drugs given at the time of examination, variables with a p value < 0.1 were chosen as independent variables. The Statistical Package for the Social Sciences software, ver. 22, was used for all statistical analyses. A p value < 0.05 was judged as statistically significant to indicate the impact of each clinical variable.

Table 2
AEDs.

	No. of subjects	Average dose (mg)
Carbamazepine	133	486 (197.9)
Levetiracetam	121	1527 (778.5)
Valproate	103	750 (360.1)
Lamotorigine	51	236 (125.8)
Topiramate	35	177 (98.8)
Perampanel	32	5 (2.38)
Phenytoin	30	288 (96.8)
Lacosamide	30	288 (92.5)
Zonisamide	22	286 (143.2)
Clobazam	19	11 (7.7)
Phenobarbital	13	92 (39.2)
Gabapentin	8	1050 (563.2)

Figures in the brackets are SD.

3. Results

1) **Incidence of EDS and sleep disorder**. Based on the results of the ESS, 21 (6.4%) of 325 PWE were judged as having EDS, while PSQI results showed that 123 (38.2%) of 322 had a sleep disorder. After excluding patients who regularly took an SPA, the rates of incidence decreased to 5.6% and 35.3%, respectively.
2) **Clinical variables with impact on ESS**. Age at the time of the examination (p = 0.018), age at epilepsy onset (p = 0.014), presence of FSWIA (complex focal seizures) (p = 0.021), and administration of lacosamide (p = 0.012) were shown to be independent variables. In multiple regression analysis, presence of FSWIA (B = 0.132, p = 0.015), age at the time of the examination (B = -0.147, p = 0.007), and administration of lacosamide (B = -0.154, p = 0.005) were each shown to have a significant impact on ESS. Thus, subjective sleepiness decreased with advancement of age as well as administration of lacosamide, and increased with the presence of FSWIA.
3) **Clinical variables with impact on PSQI**. Valproate (p = 0.020), lacosamide (p = 0.005), and SPA (p = 0.018) administration, as well as presence of generalized or bilateral tonic clonic seizures (p = 0.033), and epilepsy type other than focal and generalized epilepsy (p = 0.044) were found to be independent variables. Furthermore, logistic regression analysis revealed that both valproate (B = 1.001, p = 0.007) and lacosamide (B = -0.994, p = 0.004), and also SPA (B = 2.939, p = 0.003) had a significant impact on the presence of sleep disorder diagnosed based on the PQSI. Thus, while valproate and SPA were shown to be associated with sleep disorder, lacosamide administration tended to decrease the presence of sleep disorder.
4) **Traffic accidents** (Table 3). Among the present cohort, 239 (73.5%) possessed a valid driver's license, of whom 116 (48.5%) had a traffic accident, with that related to an epileptic seizure reported by 30 (12.5%). In our analysis of traffic accidents in total, phenobarbital (p = 0.032), levetiracetam (p = 0.016), SPD (p = 0.069), and age at the time of the examination (p = 0.001) were shown to be independent variables, and logistic regression analysis revealed that age at the time of the examination (B = 1.033, p = 0.001) and LEV (B = -1.000, p = 0.028) each had an impact on the occurrence of a traffic accident. As for traffic accidents that occurred in association with an epileptic seizure, SPD (p = 0.008), clobazam (p = 0.036), and generalized or bilateral tonic clonic seizures (p = 0.067) were found to be independent variables, while logistic regression analysis revealed that SPD was the only variable with a significant impact on a traffic accident associated with an epileptic seizure (B = 3.486, p = 0.012). When we analyzed traffic accidents unrelated to epileptic seizures, male gender (p = 0.041), gabapentin (p = 0.008),

Table 3
Traffic accidents.

Active drivers in cohort	239
MVA, yes	116
MVA, related to seizures	30
MVA, not related to seizures	83
MVA, unknown cause	3

MVA: motor vehicle accident.

phenobarbital ($p = 0.003$), and levetiracetam ($p = 0.064$) were shown to be independent variables, whereas logistic regression analysis revealed no factors with a significant impact on this dependent variable. In addition, logistic regression analysis also found no correlation of ESS score or PSQI score with any of the 3 types of traffic accident conditions analyzed.

4. Discussion

In the present PWE, there was no correlation of occurrence of a traffic accident with either EDS or sleep disorder, including accidents directly resulting from an epileptic seizure or occurring independent of such a seizure. A recent large cohort study conducted by Sundlin et al. [3] clearly demonstrated that the risk of having a traffic accident was independent of the use of AEDs, even though serious transportation accidents were more common in this population, which the authors considered to be not from excess but rather an insufficient amount of medication. The lack of positive correlation between traffic accident occurrence and sleepiness seen in the present study suggests that even though daytime sleepiness may be caused by AED ingestion, that does not have a major impact on the occurrence of such accidents. In fact, we found that use of an AED was inversely related to traffic accident occurrence. Except for advanced age, a well-known risk factor for increased motor vehicle accidents in the general population [4,5], only administration of SPA was shown to increase the risk of traffic accidents in PWE.

Most previous reports agree that the incidence of EDS as well as sleep disorders is higher in PWE than healthy individuals [2,6–9]. Furthermore, some reports have noted that successful surgical or pharmacological intervention improved daytime sleepiness and decreased sleep disorders [10,11], which also supports the correlation between epilepsy and sleep-related problems. The incidence of sleep disorder in PWE has been reported to range from 34% to 53% [8,11,12], which is similar to the present findings. Also, the lower occurrence of sleepiness in the present older population agrees well with the trend in the general population [13–15].

In contrast, opinions concerning which clinical variables have the greatest effect on EDS or sleep disorders in PWE vary greatly. Some findings support the influence of epilepsy-related variables, such as seizure frequency [1,16], and epilepsy or seizure type [1,2,16,17], while other results deny the impact of those clinical variables [6,9,18]. In the present study, FSWIA (complex focal seizures) were shown to be correlated with daytime sleepiness, which has also been noted in some previous studies [1,16,17]. However, Shen et al. (2017) in a study of Chinese PWE pointed out that the impact of epilepsy-related variables was far less powerful than other determinants, which was shown in the present study as well.

Although the effects of AEDs on daytime sleepiness as well as sleep disorders have been intensively examined, conclusions vary. Most studies have not found a negative impact of AEDs on those conditions [2,7,12,17–20], while others have reported the influence of AEDs known to promote sleep, such as clonazepam and phenobarbital [1,16], though even with those compounds the significance was marginal. In the present study, our findings showed that some compounds were actually associated with lower scores for both ESS and PSQI. Nevertheless, it is important to note that phenobarbital and clonazepam were prescribed to only a limited number of patients in our study. Differences for the variety of prescribed AEDs might explain the disparity among reports, including the present.

The association of valproate with sleep disorder found in the present study requires additional investigation. Independent from the influence of epilepsy-related variables as well as antiepileptic medications, sleep-related conditions, such as restless legs or obstructive sleep apnea, have been shown to play major roles to cause EDS and sleep disorders in several studies [6,18,21]. Valproate is known to be associated with increased body weight [22], thus it might increase the risk of obstructive sleep disorder in some Japanese PWE, who are typically not overweight [23]. In the present study we did not specifically examine affective state, which is known to be related to EDS and sleep disorders [9,16], though valproate might have been preferentially administered to some of our patients who showed a depressive mood.

In view of the various causes related to drowsiness as well as sleep disorders, a one-off measure and the scales such as used here apparently does not satisfactorily clarify the causes of these states. Clinical features such as overweight, sleep apnea syndrome, and alcohol intake before assessment might well specify the culprits which cause EDS or sleep disorder in PWE. Our method is too global to specifically address the issue.

5. Conclusion

In conclusion, neither daytime sleepiness nor sleep disorders were shown to be correlated with traffic accidents by PWE. In addition, no AED was found to promote daytime sleepiness. The notion that AED administration increases the risk of traffic accidents because of increased daytime sleepiness is widely prevalent in Japan. However, the present findings as well as those of previous reports suggest that this might be unfounded.

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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