Tiagabine

TGB inhibits neuronal and glial GABA reuptake, thereby enhancing GABA's inhibitory effect. Because TGB has a mechanism of action similar to that of VGB, concern has been raised regarding its potential to cause treatment-emergent psychosis. Sackellares *et al.* [47] conduced an ad hoc analysis of two multi-center, randomized, double-blind, placebo-controlled studies of add-on therapy of TGB, and 3 cases (0.8%) of 356 TGB-treated patients developed psychosis, compared to none of 198 placebo-treated patients. Cockerell *et al.* [15] reported two psychotic cases. Trimble *et al.* [11] reported three cases with TGB-related psychosis.

■ AEDs rarely associated with psychosis *(Table IV)*

Table IV. AEDs rarely reported to induce psychosis (single case reports are included)

1. CBZ	
Franks & Richter, 1979 [44]	1 case with psychotic symptoms exacerbated by rechallenge
Pakalnis *et al.*, 1987 [10]	4 psychotic cases with forced normalization (3 monotherapy and 1 co-therapy with VPA)
Mathew, 1988 [51]	1 case with epilepsy and mild mental handicap; psychosis developed shortly after change from VPA
McKee *et al.*, 1989 [52]	1 case with acute psychotic reaction shortly after add-on therapy
Samuimi-Ardestani *et al.*, 2008 [53]	1 TLE case with hallucinatory symptom; disappeared with discontinuation
2. FBM	
Knable & Kenneth, 1995 [54]	1 case with long-standing hypoxic brain damage developed severe psychotic symptoms
McConnell *et al.*, 1996 [55]	1 case with psychosis
3. GBP/PGB	
Crawford, 1998 [20]	1 case (0.5%) with GBP add-on therapy
Olaizola *et al.*, 2006 [56]	1 case with psychotic symptoms with PGB
4. VP	
Pakalnis *et al.*, 1987 [10]	2 psychotic cases with forced normalization (1 absence patient with monotherapy, 1 TLE patient with co-therapy with CBZ)

TLE: temporal lobe epilepsy

Carbamazepine and oxcarbazepine

These AEDs probably exert their anticonvulsant effects by sodium channel blockade, though they also have other sites of action. CBZ is approved for use in Japan for the manic state an excited state of schizophrenia. On the other hand, its prescribing information designates that the drug can provoke hallucinations and/or excitations. Rare but sporadic epilepsy cases with CBZ-related psychosis were reported as a direct side effect [44, 51-53] or forced normalization [10].

Although no previous studies have reported psychosis as a side effect of OXC, a case with Parkinson disease which developed psychotic symptoms, probably through the dopamine agonistic mechanism of OXC, was reported [57].

FBM

FBM has a number of anti-excitatory effects, which account for its anticonvulsant effects, including that on NMDA and non-NMDA excitatory amino acid receptors, as well as the inhibition of voltage-gated sodium channels. It is rarely used at present, due to serious hepatic and hematological adverse effects in some patients. Rare but sporadic epileptic patients with treatment related psychosis have been reported when receiving FEL monotherapy [55] or FBM add-on therapy [54].

Gabapentin and pregabalin

Despite being analogs of GABA, the anticonvulsant actions of GBP and PGL are likely to not be related to effects on the usual GABA binding sites. Their mechanism of action remains unknown. In the audit of the use of AEDs in a general neurology clinic carried out by Crawford [20], one case (0.5%) of 191 patients receiving GPT add-on therapy exhibited psychotic symptoms. A 44-year-old female with acute psychosis associated with marked EEG exacerbation after rapid titration of a relatively large dose of PGL was also reported [56].

Valproate

The mechanism of action of VPA may include the potentiation of GABAergic functions and inhibition of voltage-sensitive sodium channels. VPA is approved for use in Japan for the manic state and behavior disorders of epilepsy, such as dysphoria and/or aggression. Pakalnis *et al.* [10] reported two psychotic cases; one with VPA monotherapy, and one with cotherapy with VPA and CBZ. They considered these to be induced by forced normalization and not as a direct effect of VPA.

Mechanisms of AED-induced psychosis

Ketter [1] has classified AEDs into those with predominantly GABA mechanisms of action and those with antiglutamatergic effects (*Table I*). Rogawski & Loscher [2] have categorized AEDs into three categories: (1) predominant sodium (and calcium) channel activity; (2) GABA-mediated mechanisms; and (3) mixed, complex or poorly understood actions (*Table I*). Glauser [3] has grouped AEDs into four broad categories based on their major mechanisms of action: (1) voltage-gated cationic ion channel modulation; (2) augmentation of GABAergic transmission; (3) mixed GABAergic and antigultamateric actions; and (4) other than conventional actions (*Table I*). All of these classifications of AEDs do not correlate with the rate of treatment-emergent psychosis, and AED-related psychosis seems to occur irrespective of the mechanisms of action of the AED.

Matsuura [16] reported 17 patients with AED-related psychosis, including seven following rapid titration, six after acute discontinuation, and four after taking an overdose of AEDs. The follow-up study revealed that six showed recurrent psychosis without a clear relationship with any AED, and one showed a chronic course of psychosis. Schmidt *et al.* [17] analyzed 26 epileptic patients with AED-related psychosis, and reported that 8% were alternative, 4% withdrawal, and 4% intoxication from AEDs. Weintraub *et al.* [58]

reported that the average rate of AED-related psychopathology for a single AED was 8.4%, with 6.1% resulting in dose change and 4.3% resulting in AED discontinuation. It appears that psychoses with the newer AEDs occurred frequently in early clinical trials, involving a dosing schedule that subsequently appeared to be rapid, or doses that were too high. Because rapid changes in the regimen of powerful AEDs induce psychosis, it can be argued that the underlying pathomechanisms are common. A dramatic alteration in the balance between inhibitory and excitatory processes, a deficit of homeostasis in the brain, may play a key role in AED-related psychosis.

Conclusion

A selective review of the published literature in English and Japanese on AED-related psychosis was carried out. All AEDs can induce treatment-induced psychosis, regardless of the mechanisms of action, and it can be argued that the underlying pathomechanism is common. Because rapid changes in the regimen of powerful AEDs induce acute psychosis, a dramatic alteration in the balance between inhibitory and excitatory processes may play a key role. AED-induced psychosis is typically transient and responsive to a reduction or discontinuation of the drug or to antipsychotic treatment. Although it may be rare, psychosis can reoccur without relating to medication or persist chronically. When prolonged overinhibition persists, recurrent or chronic psychosis may occur. Powerful AEDs should be used with a slow titration schedule and with monotherapy, especially those prone to develop psychosis.

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Available online at www.sciencedirect.com
ScienceDirect
General Hospital Psychiatry 32 (2010) 276–283
General Hospital Psychiatry

Sleep-related problems and use of hypnotics in inpatients of acute hospital wards

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Received 6 November 2009; accepted 26 January 2010

Abstract

Objective: Although sleep disorders are highly prevalent among patients with physical disorders, only limited information is available about the actual status of sleep-related problems in inpatients of acute hospital wards. We conducted a multicenter cross-sectional observational survey investigating the prevalence of sleep disorders and use of hypnotic-sedative drugs among inpatients of acute wards in 44 general hospitals in Japan.

Method: Questionnaire-, actigraph- and observation-based sleep evaluations were simultaneously performed in 557 adult inpatients [mean age 72.8±12.8 (S.D.) years] of acute wards during a one-month period in July 2007.

Results: Of the 421 patients with data available, 22.3% had at least one of the following sleep disorders: sleep apnea syndrome, restless legs syndrome, periodic limb movement disorder and nocturnal behavior disorder. Similarly, 62.7% had insomnia, 6.9% had severe daytime sleepiness and 12.8% had other sleep-related symptoms. Only 13.8% were free of any sleep-related problem. Although 33.7% of insomnia patients were taking hypnotic-sedative drugs, 65.2% of them complained of residual insomnia symptoms.

Conclusion: The findings obtained in this study have revealed the remarkably high prevalence of sleep-related problems experienced by inpatients of acute hospital wards in Japan. Proper diagnosis of sleep disorders should be made among patients with physical disorders.

Keywords: Sleep disorders; Insomnia; Acute hospital wards; Physical illness; Hypnotic use

1. Introduction

Sleep disorders, including insomnia, sleep apnea syndrome (SAS), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), are highly prevalent and particularly common in elderly patients with physical disorders. Sleep disorders reduce patients' quality of life (QOL) by causing symptoms such as daytime sleepiness and cognitive impairment and may also exacerbate underlying disorders by inhibiting respiratory, cardiovascular and

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0163-8343/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.genhosppsych.2010.01.015

metabolic functions. In one study of older patients in a skilled-care geriatric hospital in Japan, the presence of insomnia was associated with a higher risk of mortality during the 2-year follow-up period [1].

The prevalence of these sleep disorders increases with age [2], and the high incidence of physical disorders among the elderly population is a contributing factor. Previous epidemiologic studies have revealed that the prevalence of insomnia among the general population is 10.2–48.0% [3–6], and insomnia frequently occurs in association with chronic pain disorders, respiratory diseases and neurological diseases [7]. SAS, RLS or PLMD also frequently coexists with various physical diseases including hypertension [8], ischemic heart disease [9,10], chronic kidney failure [11], iron-deficiency anemia [12] and neurological diseases such as Parkinson's disease [13]. It is also noteworthy that medications used for the treatment of sleep disorders may worsen physical disorders; for example, most standard hypnotics benzodiazepines cause *sleep apnea* by reducing the muscle tone of the upper respiratory tract during sleep [14].

The fact that physical and sleep disorders can coexist at a high frequency should always be taken into account when making an accurate diagnosis and developing a treatment strategy that provides a favorable risk-benefit balance. Nevertheless, we currently have only limited information about the actual status of sleep-related problems experienced by inpatients of acute hospital wards. Thus, the objectives of the present study were to investigate the breakdown and prevalence of sleep disorders and use of hypnotic-sedative drugs in acute ward inpatients and to identify problems in the clinical practice of sleep medicine.

2. Methods

2.1. Subjects and method

Study subjects who were 20 years of age or more were randomly selected from among the inpatients of acute hospital wards, excluding psychiatric and tuberculosis wards, of 44 general hospitals in Japan. The patients' identities were coded at each hospital ward, and then patients were randomly sampled. The investigation was carried out among 557 subjects [316 males, 241 females; mean age, 72.8±12.8 (S.D.) years; range 22–96 years] who had provided informed consent or whose family member had provided informed consent, simultaneously at all hospitals during a period of 1 month in July 2007. Each patient's primary disorder was classified according to the International Classification of Diseases and Related Health Problems Version 10 (*ICD-10*) (Table 1). The ethics committee at each research site approved the present study.

2.2. Investigation methods

The investigation was conducted over 2 days for each patient to check his or her sleep condition and details of treatment. The investigation consisted of subjective sleep evaluation using a self-administered questionnaire (Table 2), objective sleep evaluation by actigraphy, observational sleep evaluation by nursing staff and a survey of medication use as recorded in the medical records.

The questionnaire was designed to identify the presence of insomnia, SAS, RLS, PLMD, nocturnal behavior disorder (NBD), daytime sleepiness and nocturnal sleep-related symptoms. In the questionnaire, Q1–Q6 were completed by the patients, and Q7 and Q8 were completed by medical staff. Although NBD can be further divided into nocturnal delirium, REM sleep behavior disorder, behavioral and psychological symptoms of dementia and other symptoms, these disorders were not distinguished in view of the primary objective of the present study and technical restrictions.

For objective sleep evaluation, subjects were asked to wear an actigraph [Lifecorder PLUS (LC), Suzuken, Nagoya, Japan] [15] on their waist for two consecutive days for continuous recording of the intensity of activity. Total sleep time (TST; the sum of all sleep time during time in bed), total wake time (TWT; the sum of all wake time during time in bed) and sleep efficiency (SE; the percentage of TST relative to time in bed) were then calculated from the LC data. Time in bed (TIB) was defined as the time during

Table 1
Illness identified in enrolled patients

System organ/disease class	Total 557 (100%)	SAS, RLS, PLMD and NBD 94 (100%)	Insomnia			Good Sleep 63 (100%)
			Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (100%)	
Diseases of the circulatory system	140 (25.1)	20 (21.3)	7 (22.6)	44 (25.1)	9 (15.5)	15 (23.8)
Neoplasms	127 (22.8)	19 (20.2)	5 (16.1)	47 (26.9)	26 (44.8)	8 (12.7)
Diseases of the respiratory system	68 (12.2)	11 (11.7)	3 (9.7)	17 (9.7)	8 (13.8)	9 (14.3)
Diseases of the digestive system	62 (11.1)	13 (13.8)	2 (6.5)	21 (12.0)	7 (12.1)	8 (12.7)
Diseases of the nervous system	45 (8.1)	11 (11.7)	2 (6.5)	9 (5.1)	3 (5.2)	5 (7.9)
Diseases of the genitourinary system	16 (2.9)	4 (4.3)	1 (3.2)	5 (2.9)	1 (1.7)	3 (4.9)
Diseases of the musculoskeletal system and connective tissue	14 (2.5)	2 (2.1)	1 (3.2)	7 (4.0)	0 (0.0)	3 (4.9)
Certain infectious and parasitic diseases	8 (1.4)	0 (0.0)	1 (3.2)	3 (1.7)	1 (1.7)	0 (0.0)
Other diseases	77 (13.8)	14 (14.9)	9 (29.0)	22 (12.6)	3 (5.2)	12 (19.0)

SAS; sleep apnea syndrome, RLS; restless legs syndrome, PLMD; periodic limb movement disorder, NBD; nocturnal behavior disorder.

Table 2
Question items and percentages of respondents in the analyzed 421 inpatients

Items		1)	2)	3)	4)
Q1. How long did it take from light off until you went to sleep? 1) less than 15 minutes 2) 15-29 minutes 3) 30-59 minutes 4) more than 60 minutes		50.4	20.4	14.5	14.7
Q2. How many times did you awake during last night? 1) none 2) 1-2 times 3) 3-4 times 4) more than 5 times		21.4	35.9	24.9	17.8
Q3. What time did you get up this morning (h:min)?		22.6*	77.4		
Q4. Did you get up in the morning unrefreshed or nonrestored? 1) good 2) fair 3) insufficient 4) poor		38.7	37.1	19.2	5.0
Q5. Do you have daytime sleepiness?** 1) none 2)some 3) moderate 4) severe		22.8	22.8	47.5	6.9
Q6. Did you experience any of the following symptoms during last night (completed by a patient)					
Q6-a creeping sensation or restless discomfort in the limbs	1) yes 2) no	5.9	94.1		
Q6-b legs or arms jerk	1) yes 2) no	2.4	97.6		
Q6-c hot flash	1) yes 2) no	4.8	95.2		
Q6-d night sweat	1) yes 2) no	6.9	93.1		
Q6-e palpitation	1) yes 2) no	1.2	98.8		
Q6-f anxiety or panic	1) yes 2) no	1.0	99.0		
Q6-g sleep paralysis	1) yes 2) no	0.0	100.0		
Q6-h nightmare	1) yes 2) no	3.1	96.9		
Q7. Did the patient experience any of the following symptoms during last night (completed by nursing staffs)					
Q7-a loud snoring, or apnea lasting for 10 seconds or longer	1) yes 2) no	10.0	90.0		
Q7-b periodic legs or arms jerk	1) yes 2) no	2.1	97.9		
Q7-c sleep-talking, delirium or abnormal behaviors such as wandering	1) yes 2) no	6.9	93.1		
Q8. Whether or not the patient took any hypnotic-sedative drug(s) for treatment of insomnia within the past one week and the name of the drug(s) if any (completed by nursing staffs) 1) yes 2) no Name of drugs [ ]		27.6	72.4		

* Patients who woke up 30 minutes or earlier than the desired time without falling asleep again (Q3).
** answered at 2 pm.

which patients were supposed to be in bed as specified by each hospital ward, and specifically the time from "lights out" to the time at which patients were expected to wake. Mean TIB was approximately between 9 p.m. and 6 a.m. Observations by the nursing staffs on each of the wards confirmed that the patients were in bed during TIB on the evenings of the study.

For the observational sleep evaluations, several nursing staffs alternated in order to record continuously the subjects' sleep states. Opening and closing of eyes, breathing, movement and any unusual behavior of the subjects were observed and recorded at a distance so as to not disturb the subjects.

2.3. Differential diagnosis of sleep disorders

The diagnostic flow for the patients included in the investigation is shown in Fig. 1. Some of the preselected subjects (n=136) were either excluded from data analyses or could not participate due to reasons such as sudden change in physical condition such as fever, severe dementia, consciousness disturbance due to organic brain damages, need for emergency examination, hospital transfer or discharge or due to missing data on their amount of physical activity. As a result, a total of 421 patients comprised the analysis population [228 males, 193 females; mean age, 72.5±12.6 (S.D.) years; range 22-96 years]. The number of respondents for each question item is shown in Table 2.

Patients were initially examined for the presence of SAS (positive answer to Q7-a), RLS (positive answer to Q6-a), PLMD (positive answer to Q6-b or Q7-b) or NBD (positive answer to Q7-c). Those who were NOT diagnosed with SAS, RLS, PLMD or NBD were subsequently examined for the presence of insomnia. Patients were judged as having insomnia when the subjective sleep investigation indicated the presence of any one of the following:

i. Disturbances of initiating sleep (DIS): Q1, the answer indicates 30 min or more.
ii. Disturbances of maintaining sleep (DMS): Q2, the answer indicates three times or more.
iii. Early morning awakening (EMA): Q3, the answer indicates wake time 30 minutes or earlier than the desired time without falling asleep again.
iv. Non-restorative sleep (NRS): Q4, the answer indicates insufficient or poor sleep.

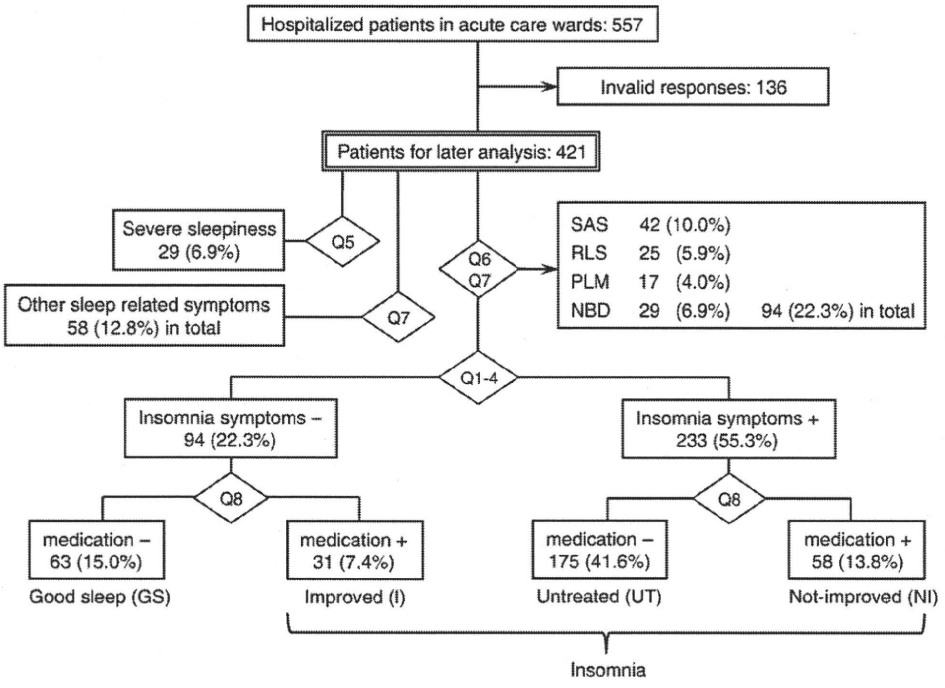

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

The subjects were also divided into the following four groups according to the presence or absence of insomnia and use or not of hypnotic-sedative drugs for insomnia treatment: the good sleep (GS) group consisting of those without insomnia and taking no medication, the improved (I) group consisting of those without insomnia and taking medication (s), the untreated (UT) group consisting of those with insomnia but taking no medication, and the not-improved (NI) group consisting of those with insomnia and taking medication(s). Of these groups, the I, UT and NI groups were grouped together and defined as the insomnia group (Fig. 1).

2.4. Daytime sleepiness

The 421 patients were examined for the presence or absence of daytime sleepiness according to the following criteria: Q5, the answer indicates the presence of moderate or severe sleepiness.

2.5. Sleep-related symptoms

The 421 patients were examined for the presence or absence of other sleep-related symptoms, such as hot flashes in the foot or body (Q6-c), night sweats (Q6-d), palpitations (Q6-e), anxiety and panic (Q6-f), sleep paralysis (Q6-g) and nightmares (Q6-h).

2.6. Statistical analysis

One-way analysis of variance followed by Tukey's multiple comparison tests was used to identify significant differences in sleep parameters (TST, TWT and SE) among the insomnia group and GS group. Sleep parameters were also compared between each sleep disorder group and the GS group using a two-tailed Student's t test. Analysis values are expressed as mean±S.D. Multiple logistic regression analysis was carried out to calculate the odds ratio (OR) and 95% confidence interval (CI) for assessing the association of primary disorders, sleep disorders and use of hypnotic-sedative drugs with severe sleepiness. Presence of severe sleepiness was used as the dependent variable, and primary disorders, sleep disorders and use of hypnotic-sedative drugs were used as independent variables. We performed multiple logistic regression analyses to control for all sociodemographic (sex and age) and other factors. Statistical significance was set at $P<.05$. All analyses were made using SPSS 11.5 for Windows.

3. Results

3.1. Prevalence of sleep disorders

The breakdown of the diagnoses of sleep disorders is shown in Fig. 1. Of the 421 inpatients, 42 (10.0%, M/F=29/13) had SAS, 25 (5.9%, 14/11) had RLS, 17 (4.0%, 11/6) had PLMD and 29 (6.9%, 19/10) had NBD. A total of 94 (22.3%) had at least one of the four sleep disorders. Seventeen patients had two sleep disorders concurrently.

Of the 421 inpatients, 58 (13.8%, NI) and 175 (41.6%, UT) complained of insomnia symptoms. A total of 264 (62.7%), including the NI, UT and I (31, 7.4%) groups were given a diagnosis of insomnia. The most common insomnia

Table 3
Comparison of objective sleep parameters determined by LC in the insomnia and good sleep patients

	SAS n=42	P	RLS n=25	P	PLMD n=17	P	NBD n=29	P	Insomnia						Good sleep n=63
									Untreated n=175	P	Improved n=31	P	Not-improved n=58	P	
TST (min)	367.6±119.2	.06	331.9±117.7	0	354.6±111.5	.01	359.8±126.1	.04	369.2±102.5	.04	400.7±118.4	n.s	399.7±91.0	n.s	409.4±102.4
TWT (min)	172.4±119.2	.05	208.1±117.7	0	185.4±111.5	.01	180.2±126.1	.04	170.3±102.3	.03	139.4±118.4	n.s	140.3±91.0	n.s	129.3±103.3
SE (%)	68.1±22.1	.05	61.5±21.8	0	65.7±20.6	.01	66.6±23.4	.04	68.4±19.0	.03	74.2±21.9	n.s	74.0±16.9	n.s	76.1±19.1

Value are expressed as mean±S.D..
P value vs. Good sleep group.
n.s; not significant.

symptom was DMS (60.1%), followed by DIS (41.2%), EMA (33.9%) and NRS (31.8%). Only 63 (15.0%) were free of the above-mentioned sleep disorders and were assigned to the GS group.

3.2. Objective sleep parameters

Sleep parameters in each sleep disorder group are summarized in Table 3. There were significant differences in TST [F(3,323)=3.24, P=.022], TWT [F(3,323)=3.28, P=.021] and SE [F(3,323)=3.31, P=.020) among the insomnia group and GS group. TST (P=.039) was significantly shorter and TWT (P=.033) and SE (P=.032) were significantly longer in the NI group than in the GS group. Patients with RLS (P<.01) and NBD (P<.05) also presented a significantly shorter TST, significantly longer TWT and significantly lower SE than those in the GS group. A similar tendency was observed for patients with SAS or PLMD (P<.06). On the other hand, we found no significant differences in the sleep parameters between the medicated group (the I or NI group) and the GS group, regardless of whether or not any subjective improvement was observed.

3.3. Daytime sleepiness

Of the 421 inpatients, 229 (54.4%) experienced moderate to severe sleepiness and 29 (6.9%) experienced severe sleepiness. Severe sleepiness was commonly observed in those with sleep disorders; it was most commonly observed in patients with multiple sleep disorders (27.8%, 5/18), followed by those with PLMD (18.2%, 2/11), SAS (17.9%, 5/28) and NBD (17.7%, 3/17). Multiple logistic regression analysis revealed that SAS (adjusted OR=3.78, 95% CI, 1.24–11.53, P<.05) and PLMD (adjusted OR=5.93, 95% CI, 1.50–23.4, P<.05) showed a significantly positive association with the presence of severe sleepiness.

3.4. Other sleep-related symptoms

Of the 421 inpatients, 19 (4.5%, M/F=7/12) had hot flashes, 29 (6.9%, 13/16) had night sweats, 5 (1.2%, 1/4) had palpitations, 4 (1.0%, 2/2) had anxiety or panic and 13 (3.1%, 7/6) had nightmares. None of the patients experienced sleep paralysis.

3.5. Prevalence of use of hypnotic-sedative drugs

Of the 421 inpatients, 116 (27.6%) were taking some kind of hypnotic-sedative drug for the treatment of insomnia symptoms. The breakdown of the prescribed drugs was as follows: benzodiazepine hypnotics including zolpidem and zopiclone accounted for 73.2% (26.1% for ultrashort-acting, 30.6% for short-acting and 16.5% for intermediate-acting), benzodiazepine anxiolytic accounted for 5.8%, antipsychotics accounted for 15.6% and other drugs accounted for 5.2% of all prescribed drugs. In the insomnia group, those receiving medication therapy for insomnia only accounted for 33.7% (the I+NI group). Two thirds of the patients receiving medication therapy (65.2%, corresponding to the NI group) complained of persistent insomnia symptoms. In addition, 36.0% of RLS patients, 29.4% of PLMD patients, 26.2% of SAS patients and 17.2% of NBD patients were taking at least one of the above hypnotic-sedative drugs.

4. Discussion

This is the first multicenter study investigating the prevalence of sleep disorders in inpatients of acute wards in general hospitals. Sleep disorders are extremely common disorders among community residents, and are even more so among patients with underlying physical diseases as in the subjects of the present study. Insomnia, as well as other sleep disorders, while frequently thought to be transitory or secondary to a physical disease, can become prolonged without appropriate treatment in the early stages. Furthermore, chronic sleep disorders can exacerbate lifestyle-related diseases such as hypertension and diabetes, and increase the risk of psychiatric symptoms such as depression and anxiety, not to cause subjective distress [16,17]. Many sleep disorders go undetected and are not appropriately treated in clinical practice. Therefore, this study was conducted to alert practitioners of sleep disorders to this situation, by shedding more light on their current status in general medical practice.

In the present study, we investigated the prevalence of sleep disorders and the use of hypnotic-sedative drugs in 421 inpatients with mean age of 72.5 years by questionnaire-, actigraph- and observation-based sleep evaluations, and have revealed a high prevalence of diverse types of sleep disorders

in the study population. SAS, RLS, PLMD, NBD and insomnia, in particular, were highly prevalent (10.0, 5.9, 4.0, 6.9 and 62.7%, respectively). The inpatients also suffered from various sleep-related symptoms (1.0–6.9%, except for sleep paralysis), which are common conditions with physical disorders and which could cause disrupted sleep [18–21]. In fact, the patients with these sleep disorders also showed poor sleep parameters recorded by actigraphy, which objectively indicates that they have poor-quality sleep during the night. Consequently, of the 421 patients, only 13.8% were free of any type of sleep disorder diagnosed, severe daytime sleepiness or sleep-related symptoms, revealing that sleep-related problems are very common clinical problems among inpatients of acute hospital wards.

Due to restrictions on the disclosure of personal information, the only information available regarding the underlying diseases of the patients was the names of the primary diseases according to the major classification of the *ICD-10*. We were thus unable to analyze respective medical conditions that are commonly associated with these sleep disorders, such as chronic pain, cardiovascular diseases, chronic renal failure, hemodialysis and iron deficiency anemia.

The prevalence of SAS and RLS is generally high in elderly people and patients with physical disorders. However, even though the mean age of our patients was high (72.5 years) and they had physical disorders in the exacerbation phase, contrary to our expectations, the prevalence of SAS and RLS was not higher in the study population than in community dwellers of previous studies. For example, the prevalence of SAS in middle-aged to elderly people has been shown to be 9–10% in males and 4–10% in females [22,23], which is comparable to that in the present study population (10% in the entire population, 12.7% in males, 6.7% in females). In the present study, patients were defined as having SAS if they reported loud snoring or apnea lasting for 10 seconds or more, because loud snoring is the most prominent symptom of upper airway resistance syndrome, which is included in the category of SAS [7,24]. Nevertheless, the prevalence of SAS patients including those who snored loudly in the present study was similar to that in the general population. Similarly, a large-scale survey which employed a self-administered questionnaire and used a definition of RLS similar to that in the present study has reported that the prevalence of RLS among Japanese people aged 70 years or more is 4.1% (3.4% in males, 4.6% in females), which is practically identical to that in the present study (5.9% in total, 6.1% in males, 5.7% in females) [25]. Furthermore, the frequency of NBD was as low as 6.9%, despite the occurrence rate of delirium per admission varying between 11 and 42% [26]. The low NBD frequency of the present study compared to that of all previous studies is thought to be because patients with severe physical conditions or with organic brain damages were excluded from the analyses.

In many of the epidemiologic studies on the prevalence of sleep disorders, sleep evaluation is performed during a period of one week to one month. The fact that sleep evaluation in this study was performed on a single night might have held down the prevalence of sleep disorders. However, since the physical status of the inpatients of acute hospital wards can change in a very short period of time and their sleep condition is also subject to change, we assumed that the results obtained from a long investigation period would not properly reflect the actual status of their sleep-related problems. Extension of the duration for determining the presence or absence of sleep disorders may result in a dramatic increase in the prevalence of the sleep disorders in inpatients of acute hospital wards.

Patients with physical disorders, especially with advanced age, are generally vulnerable to insomnia [27–29]. We have found that approximately two thirds (62.7%) of the representative patients in acute wards in Japan are suffering from insomnia. It was confirmed not only from the subjective complaints of patients but also from the objective sleep evaluation that the quality of sleep for patients with insomnia receiving no treatment or who had other sleep disorders was significantly lower than that for patients in the GS group (Table 3). A survey among 1500 community dwellers aged 55–84 years in the United States has demonstrated that the quality of sleep decreases in proportion to an increase in the number of physical disorders suffered [27]. Several studies have also reported a high prevalence (34–69%) of insomnia in outpatients of primary care clinics or regular inpatients with acute or chronic physical disorders [30–33]. The findings of the present study for acute ward inpatients are consistent with those obtained in the previous studies in spite of shorter-term sleep evaluation.

In many cases of sleep disorders, daytime sleepiness often occurs to compensate for low-quality sleep during the night. In the present study, 47.5% of the patients experienced mild or severer sleepiness and 6.9% experienced severe sleepiness, which was particularly high in those with multiple sleep disorders, including SAS, RLS, PLMD and NBD. The results of multiple logistic regression analysis indicated that severe sleepiness is significantly associated with SAS and PLMD, and not with an underlying disease or type of hypnotic-sedative drug.

Only one-third (33.7%) of the patients with insomnia included in the present investigation received treatment for insomnia symptoms. In addition, two-thirds (65.2%) of the patients receiving medication therapy complained of residual insomnia symptoms. The relatively low frequency of patients prescribed hypnotic-sedative drugs in the present study, which is very similar to that reported in the Meissner's study [30], suggests the possibility that physicians are not fully aware of the presence of insomnia in their patients.

The prescribed drugs mainly consisted of benzodiazepine hypnotics including intermediate-acting agents and antipsychotics. Caution should always be exercised when

using these hypnotic-sedative drugs in inpatients with physical disorders, especially in elderly patients. This is because elderly patients present a poor risk-benefit balance for hypnotic-sedative drugs due to such reasons as decreased drug metabolizing capacity, increased drug sensitivity, risk of fall and fracture or suppressed mental function, and worsening of underlying diseases induced by medication [34–37].

Moreover, administered hypnotic-sedative drugs may be ineffective or even worsen underlying diseases unless sleep disorders are properly diagnosed. In fact, 23.8% of the patients with SAS were prescribed hypnotic-sedative drugs including benzodiazepines and 36.0% of the patients with RLS were taking hypnotic-sedative drugs other than clonazepam. These results suggest that medications that are not necessarily appropriate for treatment of individual patients' sleep disorders are often selected in actual clinical practice, possibly causing a reduction in the patients' ADL and QOL.

Several limitations should be noted when interpreting the results of the present study. First, as elderly patients aged 65 years or more accounted for a large portion (76.0%) of the 421 inpatients, it is speculated that the high prevalence of sleep-related problems observed in the patients of the present investigation were associated with not only sleep disorders attributable to physical disorders but also age-related changes in sleep property.

Second, one-fourth (24.4%) of the initially enrolled 557 patients were excluded. Patients who were unable to answer questions on the day of the survey because of a change in their physical condition (e.g. fever, consciousness disturbance or need for emergency examination) or those patients with missing data due to interruptions in LC data collection were excluded. Some of these excluded patients might have developed some type of sleep disorder during their stay in hospital.

Third, insomnia defined in the present study is different from insomnia that meets the general criteria of the International Classification of Sleep Disorders, second edition (ICSD-2) [7], because we did not consider the presence or absence of "daytime impairment related to the nighttime sleep difficulty". This investigation item was not included in the present study because it was difficult to determine whether the patients' diverse psychosomatic symptoms observed during the daytime were attributable to insomnia or physical disorders.

Fourth, the questionnaire employed in the present study has not been validated. A set number of items taken from the original were configured so as to reduce the burden on inpatients who were in poor physical condition. Therefore, the questionnaire can only suggest the possibility of certain disorders such as SAS, PLMD and RLS; it does not predict the presence of these disorders with high accuracy. However, the frequency of sleep disorders and the percentage of patients exhibiting symptoms of insomnia found in the present study closely resemble the data of several other studies. This is thought to be indirect evidence that, to a certain degree, the survey items work effectively to detect patients suffering from sleep disorders.

Fifth, the sleep/wake scoring algorithm used for the LC data in the present study has been validated for a sample of healthy young subjects [15], but not for elderly subjects with physical disorders, as in the present study's sample. However, as the results demonstrate, meaningful differences were detected in the sleep parameters calculated with this algorithm for total sleep time, total wake time, and efficiency of sleep between the UT group with insomnia and the GS group. Given this, the clinical application of the LC and sleep/wake scoring algorithm for the subjects of the present study can be considered a sound approach to a certain degree.

5. Conclusion

In the present study, which initially involved 557 inpatients who had been admitted to acute hospital wards in 44 general hospitals, we have revealed an extremely high prevalence of sleep disorders using subjective and objective sleep evaluation scales, and have also indicated several problems in the current practice of sleep medicine. Proper diagnosis of sleep disorders should be made while being aware of the high prevalence of sleep disorders among elderly patients with physical disorders, and a treatment strategy that provides a favorable risk-benefit balance must be developed.

Acknowledgments

This study was supported by a Grant-in-Aid for Cooperative Research from the Ministry of Health, Labor, and Welfare of Japan (H19-kokoro-ippan-013, H20-tyojyu-ippan-001).

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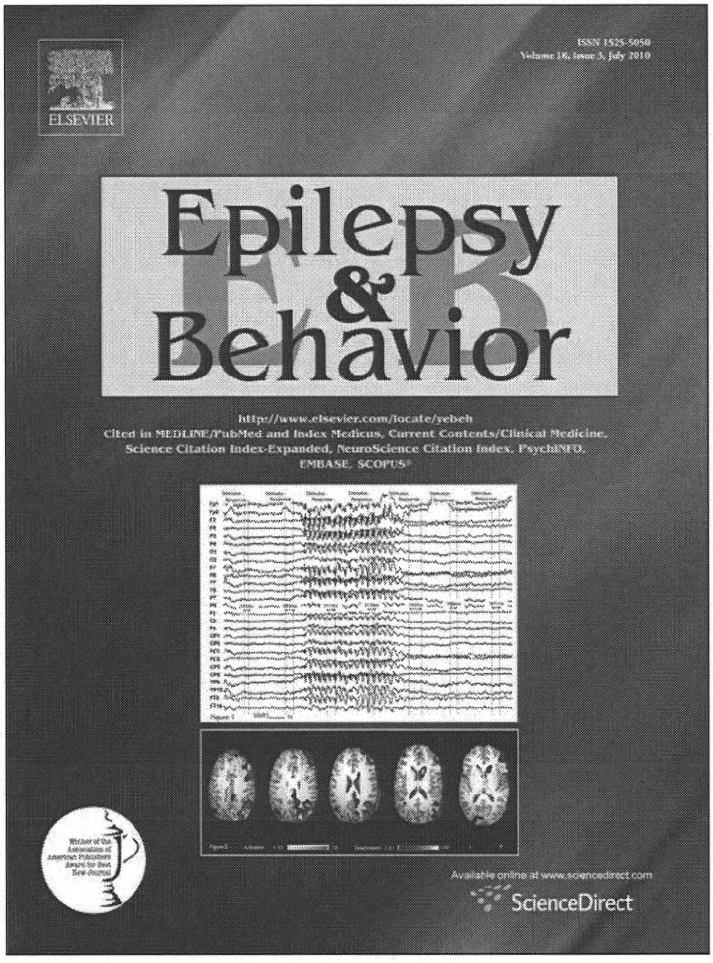

Epilepsy & Behavior 18 (2010) 218–222

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Two forms of déjà vu experiences in patients with epilepsy

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ARTICLE INFO

Article history:
Received 1 February 2010
Received in revised form 15 February 2010
Accepted 17 February 2010
Available online 21 May 2010

Keywords:
Epilepsy
Neuropsychiatry
Psychology
Déjà vu
Seizure recognition

ABSTRACT

Persons with epilepsy experience déjà vu phenomena with or without seizure recognition. Déjà vu experiences are also common mental phenomena in nonclinical individuals. The purpose of this study was to clarify two forms of déjà vu experiences in persons with epilepsy. Déjà vu experiences of 312 patients with epilepsy and 402 nonclinical individuals were evaluated using the Inventory of Déjà vu Experiences Assessment. In the patients with epilepsy, characteristics of déjà vu experiences with seizure recognition (SR form) were compared with those experiences with no seizure recognition (NSR form). The incidence (63.1%) of déjà vu experiences in patients with epilepsy was significantly lower than that (76.1%) of nonclinical individuals ($\chi^2 = 14.2$, $P = 0.000$). Among the patients with epilepsy, 55.6% had the NSR form and 24.0% had the SR form. Those with the NSR form manifested fewer psychopathological characteristics than did those with the SR form. Patients tended to view the SR form more negatively (i.e., frightened, uncomfortable, or disturbed) than the NSR form. The NSR form was significantly associated with idiopathic generalized epilepsies, less frequent antiepileptic drug administration, and no mesial temporal sclerosis. Although there was a significant association between the frequency of the SR form and patients' habitual seizures, the frequency of the NSR form was not associated with the frequency of the patients' habitual seizures. Persons with epilepsy experience two forms of déjà vu which are differently associated with their seizure recognition.

1. Introduction

Patients with epilepsy experience déjà vu as ictal phenomena either spontaneously [1,2] or artificially in response to electrical stimulation [3–5]. Gastaut [6] described epileptic illusions of déjà vu as ictal manifestations, resulting from discharge in the temporal cortex, during which previously unknown objects and situations, even though clearly perceived, appear familiar. Because déjà vu experiences have been classified as simple partial seizures [7], any déjà vu experiences of patients with epilepsy are likely to be regarded as epileptic phenomena.

Déjà vu experiences are also common mental phenomena in patients with nonepileptic neuropsychiatric diseases [8–10] or even in nonclinical individuals [11–13]. In recent community studies, approximately 70% of the nonclinical individuals reported some déjà vu experiences [14,15]. Patients with epilepsy can have nonepileptic subjective events as well as epileptic subjective events [16]. Although some authors have reported that déjà vu experiences occur more commonly during interictal periods than during seizures [17], no quantitative data have been presented. It is of interest whether patients with epilepsy experience various forms of déjà vu. Are some déjà vu experiences of patients with epilepsy similar to those of people without epilepsy?

The purpose of this study was to clarify whether patients with epilepsy experience different forms of déjà vu. As patients' recognition is an indispensable condition in the study of subjective mental experiences, such as psychic seizures, we investigated déjà vu experiences with or without the patients' seizure recognition.

2. Methods

2.1. Definitions

Déjà vu is defined as "any subjectively inappropriate impression of familiarity of a present experience with an undefined past" [18]. Déjà vu experiences as epileptic seizure phenomena are defined as simple

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doi:10.1016/j.yebeh.2010.02.016

partial seizures with psychic symptoms [7]. In the current study, déjà vu experiences recognized as habitual seizures by patients are classified as the seizure recognition (SR) form and those recognized as not related to seizure phenomena by patients are classified as the non-seizure recognition (NSR) form.

2.2. Participants

Three hundred twelve consecutive patients with epilepsy were recruited from six epilepsy outpatient clinics in Japan (Adachi Mental Clinic; National Centre Hospital for Mental, Nervous and Muscular Disorders; Tenshi Hospital; Nihon University Hospital; Aichi Medical University Hospital; and Musashino Kokubunji Clinic). To compare the prevalence of déjà vu experiences, we used 402 of the 479 nonclinical individuals who participated in our prior studies of déjà vu experiences [8,14,19,20]. These control subjects were matched with respect to age, sex, and education to the patients with epilepsy in the current study. These participants (i.e., users of community services or workers in private companies) had neither neurological nor psychiatric illnesses. All participants gave informed consent to participate in the study.

2.3. Research items

The following demographic features were evaluated in both the patients with epilepsy and the nonclinical individuals: age at the time of examination, sex, and total years of education. The patients with epilepsy were evaluated further to determine (1) age at onset of epilepsy; (2) duration of epilepsy; (3) epilepsy type (generalized epilepsy (GE) and partial epilepsy (PE) were diagnosed on the basis of seizure characteristics and clinical examinations in accordance with the international epilepsy classification [21]; PE was divided into temporal lobe epilepsy, frontal lobe epilepsy, parietal lobe epilepsy, and occipital lobe epilepsy); (4) frequency of seizures in accordance with the frequency guidelines previously reported [22]; (5) number of antiepileptic drugs (AEDs) taken; (6) lateralization of EEG abnormalities in interictal scalp EEG recordings [22]; (7) presence of mesial temporal sclerosis (MTS) detected by MRI according to our routine protocol and assessed qualitatively [23,24].

2.4. Assessment of déjà vu experiences

The Japanese version of the Inventory of Déjà vu Experiences Assessment (IDEA) [19,25] was used to assess déjà vu phenomena. All participants completed IDEA Part A (IDEA-A), which contains nine items and covers the frequency of déjà vu and its related psychobehavioral experiences (i.e., derealization, jamais vu, precognitive dreams, depersonalization, paranormal quality, remembering dreams, travel frequency, and daydreams). Although the IDEA is well standardized and validated in patients with epilepsy [19], we slightly modified it to specify the patient's seizure recognition. We conditioned on all of the IDEA-A items that the experiences occurred without the patient's seizure recognition. Furthermore, we added three items (items A10–A12, see Appendix A) to ask specifically about the SR form. Both patients with epilepsy and nonclinical individuals who experienced the NSR form (IDEA-A1) completed IDEA Part B (IDEA-B), which covers characteristics of the NSR form. Patients who had experienced the SR form (IDEA-A10) completed IDEA Part C (IDEA-C), which uses the same items from IDEA-B for the SR form. Test–retest reliability of the IDEA-A, -B, and -C items with the additional conditions and questions was evaluated and proven to be sufficient ($n=44$, interval 3–6 months): IDEA-A (intraclass correlation coefficient [ICC] = 0.481–0.949, $P=0.000$–0.017), IDEA-B (ICC = 0.493–0.886, kappa measure of agreement [κ] = 0.331–1.000, $P=0.000$–0.169), and IDEA-C (ICC = 0.449–0.892, κ = 0.400–1.000, $P=0.000$–0.166) (see Appendix A for details). Self-administered assessments were all conducted under clear consciousness with no distinct seizure activity for 12 hours or longer.

2.5. Analysis

For demographic data, one-way analysis of variance, χ^2 test, or Fisher's exact test was used. For the raw IDEA score data, differences and correlations were analyzed with the Mann–Whitney U test, χ^2 test, or Fisher's exact test. The Wilcoxon signed ranks test was used to analyze an individual's paired nonparametric variables. The relationship between each IDEA score and clinical factors was analyzed with the Spearman rank correlation coefficient. The binominal test or χ^2 goodness-of-fit test was used for comparisons of percentages. To test the reliability of the modified questionnaire, ICCs and κ values were used. A P value <0.05 was considered significant. The Bonferroni correction was used for multiple comparisons when necessary. SPSS Version 14.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Characteristics of the study participants

Our population of patients with epilepsy comprised 164 men and 148 women, and the age at examination ranged from 17 to 66 years (mean = 34.7, SD = 10.9). Total years of education ranged from 9 to 19 (mean = 13.5, SD = 2.0). Age at onset of epilepsy ranged from 0 to 56 years (mean = 15.3, SD = 9.5). Duration of epilepsy ranged from 0 to 49 years (mean = 19.4, SD = 11.6). With respect to type of epilepsy, 49 patients had GE and 263 had PE. All of the patients with GE had idiopathic generalized epilepsy (IGE). Among the patients with PE, 143 had temporal lobe epilepsy (TLE), 79 had frontal lobe epilepsy (FLE), 16 had parietal lobe epilepsy {PLE), and 25 had occipital lobe epilepsy (OLE). Seizure frequency was classified as daily in 12 patients, weekly in 48 patients, monthly in 83 patients, yearly in 95 patients, less than yearly in 40 patients, and seizure freedom in 34 patients. The number of AEDs taken ranged from 0 to 5 (mean = 1.9, SD = 1.0). The main AEDs taken were carbamazepine in 186, valproic acid in 93, phenytoin in 110, phenobarbital in 78, zonisamide in 27, and benzodiazepines in 93 patients. EEG abnormalities were left-sided in 103, right-sided in 92, and bilateral in 109 patients, with no lateralization in 8 patients. MRI studies ($n=309$) revealed left MTS in 29, right MTS in 20, and bilateral MTS in 10 patients, and were unremarkable in 250 patients.

The 402 nonclinical individuals comprised 199 men and 203 women and this distribution was similar to that of the patients ($\chi^2=0.66$, $P=0.451$). Age at the time of examination ranged from 15 to 66 years (mean = 35.4, SD = 11.1), which was similar to that of the patients with epilepsy ($F=0.73$, $P=0.393$). Total years of education ranged from 9 to 18 (mean = 13.7, SD = 2.0), which was equivalent to that of the patients ($F=1.9$, $P=0.173$).

3.2. Frequency of the NSR and SR forms

In total, 197 (63.1%) of the 312 patients with epilepsy had some déjà vu experiences, whether NSR, SR, or both, a rate significantly lower than that of the nonclinical individuals (306/402, 76.1%) ($\chi^2=14.2$, $P=0.000$). One hundred seventy-three (55.6%) had the NSR form, the frequency of which was significantly lower than that of the nonclinical individuals ($\chi^2=34.0$, $P=0.000$). In addition, 75 (24.0%) had the SR form (IDEA-A10); the frequency of the SR form was weekly in 5 patients, monthly in 11 patients, yearly in 23 patients, and less than yearly in 20 patients; 16 patients had experienced the SR form previously but not within the last 3 years. Fifty-one (16.3%) patients had both NSR and SR forms.

3.3. Phenomenological differences between the NSR and SR forms

Among the 51 patients who had both NSR and SR forms, 43 (84.3%) felt there were some differences between the two forms according to their answers to IDEA-A12 (mean = 3.7, SD = 0.9, median = 4, $n = 51$). Phenomenological characteristics of the NSR form (as evaluated with IDEA-B, $n = 309$; two patients failed to answer) were compared with those of the SR form (IDEA-C, $n = 75$) (Table 1). Although the SR form occurred until recently and did so frequently at nighttime, the NSR form rarely occurred recently and showed no tendency of time of occurrence. The NSR form had significantly fewer psychopathological features (i.e., precognition, depersonalization, and derealization) than the SR form. Patients tended to view the SR form more negatively (i.e. frightened, uncomfortable or disturbed) than the NSR form. In addition, patients felt significantly more indifferent to or pleased about the NSR form than the SR form.

3.4. Relationship between NSR/SR forms and demographic characteristics

Age at examination was related significantly to frequency of the NSR form both in the patients with epilepsy ($r = -0.150$, $P = 0.008$) and in the nonclinical individuals ($r = -0.368$, $P = 0.000$). Frequency of the SR form in patients with epilepsy was not related to age at examination ($r = 0.054$, $P = 0.340$).There was no difference between the sexes in the frequency of the NSR form both in the patients with epilepsy ($z = -0.33$, $P = 0.744$) and in the nonclinical individuals ($z = -0.98$, $P = 0.329$). Sex was not related to the ictal form ($z = -0.14$, $P = 0.886$). Although duration of education was significantly related to the frequency of the NSR form in nonclinical individuals ($r = 0.116$ $P = 0.020$), such a relationship was not observed in the patients with epilepsy ($r = 0.008$, $P = 0.892$). The frequency of the SR form was related significantly to duration of education ($r = -0.150$, $P = 0.008$).

3.5. Relationship between NSR/SR forms and characteristics of epilepsy

Epilepsy characteristics relative to the NSR and SR forms are summarized in Table 2.

3.5.1. Age at onset of epilepsy and duration of illness

The frequency of the NSR form did not correlate with either age at onset or duration of epilepsy. In contrast, the frequency of the SR form correlated significantly with earlier age at onset of epilepsy and longer duration of epilepsy.

3.5.2. Epilepsy type

The NSR form occurred more frequently in patients with GE than in those with PE, whereas the SR form occurred more frequently in patients with PE than in those with GE. Among the patients with PE, the NSR form was observed in 68 of 143 (47.6%) with TLE, 46 of 79 (58.2%) with FLE, 10 of 16 (62.5%) with PLE, and 15 of 25 (60.0%) with OLE ($\chi^2 = 3.64$, $P = 0.304$). The SR form was observed in 45 (32.2%) with TLE, 18 (22.8%) with FLE, 2 (12.5%) with PLE, and 6 (24.0%) with OLE ($\chi^2 = 3.98$, $P = 0.268$).

3.5.3. Seizure frequency

The NSR form (median, less than yearly) occurred less frequently than did each individual's habitual seizures (median, yearly) ($z = -4.29$, $P = 0.000$). The frequency of the NSR form did not correlate significantly with the frequency of habitual seizures, whereas the frequency of the SR form correlated significantly with the frequency of seizures, particularly in those with partial seizures (complex partial seizures: $r = 0.219$, $P = 0.000$; simple partial seizures: $r = 0.275$, $P = 0.000$, $n = 263$).

3.5.4. Antiepileptic drug treatment

Patients with the NSR form took fewer AEDs (mean = 1.8, SD = 1.0) than those without the NSR form (mean = 2.1, SD = 1.0) ($F = 6.90$, $P = 0.009$), whereas patients with the SR form took a larger number of AEDs (mean = 2.1, SD = 1.0) than did those without (mean = 1.9, SD = 1.0) ($F = 3.86$, $P = 0.050$). Number of AEDs taken correlated significantly with the frequency of the NSR or SR form.

Table 1
Differences in phenomenologic characteristics between No Seizure Recognition (NSR)/ Seizure Recognition (SR) forms in epilepsy patients.

Nominal variables	NSR form (n = 171)	SR form (n = 75)	X^{2*}	P
B2-C1 Retrocognition			2.56	0.280
none	98	38		
vaguely	65	31		
clearly	8	6		
B3-C2 Elapsed period of time			28.6	**0.000***
5 years or more ago	44	16		
1-5 years ago	52	17		
6 months-1 year ago	20	17		
2-6 months ago	15	3		
1-2 months ago	17	7		
1 month or less	23	15		
B4-C3 Duration			4.31	0.221
1 second or less	18	5		
seconds	115	47		
minutes	31	20		
hours	7	3		
B5-C4 Pervasiveness			5.62	0.060
totally	20	8		
partially	57	16		
/various	94	51		
B6-C5 Time of day			22.1	**0.001***
no tendency	135	52		
daytime	27	10		
evening	6	9		
in bed	3	4		
B7-C6 Precognition			14.7	**0.007***
none	127	48		
less than 1 year	31	13		
yearly	7	6		
monthly	4	6		
weekly	2	2		
B8-C7 Depersonalization			11.6	**0.029***
non	125	44		
vague feeling it was not happening to me	13	9		
clear feeling it was not happening to me	2	2		
vague feeling I was looking at myself	20	16		
clear feeling I was looking at myself	11	4		
B9-C8 Repetition			3.54	0.469
exactly the same	11	2		
almost exactly the same	20	9		
the same	8	6		
approximately the same	25	12		
vaguely the same	107	46		
B10-C9 Derealization			11.6	**0.023***
none	116	38		
a little unreal	21	9		
vaguely unreal	25	19		
unreal	6	5		
totally unreal	8	4		
B11-C10 Effects (yes/no)				
a. Indifference	75/96	16/59		**0.000****
b. Alarm	28/143	34/41		**0.000****
c. Reassurance	14/157	5/70		0.439
d. Pleasure	31/140	4/71		**0.001****
e. Oppression	51/120	50/25		**0.000****
f.. Surprise	76/95	25/50		0.039
g. Disturbance	38/133	35/40		**0.000****

NSR form was assessed with the IDEA-B and SR form was assessed with the IDEA-C.
* With chi-squared goodness-of-fit test, **Binominal test with Bonferroni correction, 0.05/7 = 0.007**.

Table 2
Relations between clinical characteristics and frequency of NSR/SR forms in epilepsy patients.

Variables	NSR form	SR form
Age of onset of epilepsy	R = -0.072/p = 0.208	R = -0.136/p = 0.017
Duration of epilepsy	R = -0.092/p = 0.103	R = 0.147/p = 0.009
Epilepsy type	GE 34/49 : PE 139/263 $X^2 = 4.57/p = 0.032$	GE 4/49 : PE 71/263 $X^2 = 8.02/p = 0.005$
Seizure frequency	R = -0.064/p = 0.256	R = 0.286/p = 0.000
Number of antiepileptic drugs	R = -0.149/p = 0.009	R = 0.115/p = 0.043
Lateralization of EEG abnormalities (n = 309)	L 54/103 : R 47/92 : Bil 71/114 $X^2 = 3.24/p = 0.137$	L 23/103 : R 29/92 : Bil 23/114 $X^2 = 3.88/p = 0.114$
MTS in MRI studies (n = 309)	Exist 26/59 : Nil 146/250 $X^2 = 3.97/p = 0.046$	Exist 19/59 : Nil 56/250 $X^2 = 3.88/p = 0.143$

Spearman rank correlation coefficient (R), Chi-square test (X^2).
GE; generalized epilepsies, PE; partial epilepsies, L; left, R; right, Bil; bilateral, MTS; mesial temporal scrolosis.

3.5.5. Lateralization of EEG abnormalities

Lateralization of EEG abnormalities was not significantly associated with frequency of the NSR and SR forms.

3.5.6. Mesial temporal sclerosis for MRI

Patients with MTS exhibited the NSR form less frequently than those without MTS, whereas there was no significant association between the SR form and MTS. The NSR form occurred in 10 (34.5%) of 29 patients with left MTS, 10 (50.0%) of 20 with right MTS, 6 (60.0%) of 10 with bilateral MTS, and 146 (58.4%) of 250 without MTS ($\chi^2 = 6.37$, $P = 0.090$). The SR form occurred in 7 (24.1%) with left MTS, 8 (40.0%) with right MTS, 4 (40%) with bilateral MTS, and 56 (22.4%) without MTS ($\chi^2 = 4.51$, $P = 0.218$).

4. Discussion

4.1. The distinction of déjà vu experiences

Our patients with epilepsy experienced different forms of déjà vu. The distinction of déjà vu experiences with patients' seizure recognition was validated by several findings. First, most of our patients differentiated with high reliability whether their déjà vu experiences were related to seizures or not. Their emotional responses to the two forms differed significantly. In general, patients' self-recognition of their habitual seizures is highly reliable [26]. Second, clinical characteristics (e.g., age at onset of epilepsy, epilepsy type, habitual seizure frequency, AEDs taken, and MTS) also differed between patients with the NSR form and those with the SR form. Third, the incidence of the NSR form (55.6% of all patients with epilepsy and 52.9% of those with PE) is much higher than expected for ictal phenomena, given that the reported incidence of all simple psychic seizures in patients with PE ranged between 10 and 25% [27–29]. Fourth, like déjà vu experiences in nonclinical individuals [15,30], the frequency of the NSR form decreased as age advanced, whereas the frequency of the SR form was not associated with age.

4.2. Frequency of the two forms of déjà vu in patients with epilepsy

Approximately 55% of patients with epilepsy were reported to have the NSR form, and this value is significantly lower than that for the nonclinical participants. Even when both the NSR and SR forms were considered, only 63.1% of the patients with epilepsy had experienced déjà vu. Although the reported incidence of déjà vu in patients with epilepsy ranges very widely from 23 to 85% [2,17,18,31], most studies have reported a lower incidence compared with that of the general population [15]. Interestingly, the frequency in our patients with epilepsy was similar to that of patients with other neuropsychiatric disorders [8,10]. Because ordinary déjà vu phenomena appear to develop as part of normal brain activity [14], patients with brain dysfunction may experience déjà vu less frequently.

4.3. NSR form and brain pathologies

The NSR form often occurred in patients without serious brain pathologies. Seventy percent of our patients with IGE had the NSR form, an incidence similar to that of the nonclinical individuals. In contrast, in our patients with PE (particularly those with MTS) the incidence of the NSR form was low, similar to that (42%) of patients with severe cerebral pathology [10]. Patients with IGE appear to have minor brain pathologies [32,33], whereas those with PE often have rather distinct cerebral pathologies [34]. Likewise, lower frequency of seizures, smaller number of AEDs taken, and absence of MTS were also associated with higher frequencies of déjà vu. These findings support the idea that the damaged brain generates the NSR form less frequently than the undamaged brain.

In the current study, patients with MTS experienced the NSR form infrequently. Patients with TLE had the lowest incidence of the NSR form among the patients with PE; however, this finding was not statistically significant. Although many studies have associated a network of temporal lobe structures with the SR form [1,3,34–36], there is no report of any focal brain lesion associated with the NSR form. Our present findings may indicate that undamaged temporal lobe structures play an essential role in generating the NSR form.

4.4. SR form and psychopathology

The SR form had more dissociative features, that is, depersonalization, derealization, and precognition, than did the NSR form. In general, déjà vu experiences in nonclinical individuals are rarely associated with pathological dissociations [20]. Our patients with epilepsy regarded the SR form as more unpleasant than the NSR form. This may be due in part to memories of subsequent serious seizure events. In addition, when patients with PE experience déjà vu ictally, the mesial temporal lobe structures may be involved with intense epileptic activity, and additional unpleasant sensations may be evoked.

4.5. Limitations

Several limitations of the current study should be considered. First, although the NSR form had many characteristics unrelated to severe epileptic conditions, it can still be considered a kind of unrecognized seizure. We have not confirmed the reported déjà vu experiences with EEG recordings or other examinations. There are considerable difficulties in capturing the NSR form with casual EEG recordings. Unlike frequent seizures in epilepsy surgery candidates, the NSR form occurs very infrequently; approximately 90% of the patients had these experiences yearly or less frequently. Even if these experiences could be captured, the NSR form would most likely produce no EEG changes. However, even the SR form can produce minimum EEG changes; 70–80% of independent simple psychic seizures yield unremarkable findings on intensive video/scalp EEG monitoring [37,38]. Second, although we used well-standardized assessment instruments, some subjective experiences could not be evaluated accurately. In particular, patients with epilepsy, when compared with nonclinical individuals, are likely to have memory dysfunction which can cause a specious reduction in such phenomena. Even in nonclinical individuals, the older the individual and the more advanced the decline in memory function, the less frequently déjà vu experiences are observed [14,15]. Subtle non-ictal phenomena may be dismissed more easily in comparison with intense ictal phenomena. Some patients may have forgotten their non-ictal experiences because of memory disturbances. However, whereas most non-ictal experiences

examined with the IDEA-A did not differ in frequency between patients and controls, it is unlikely that the patients dismissed or forgot only the déjà vu experiences. Nevertheless, further research on memory function and the NSR form is required. Third, as space was limited, we concentrated on clarification between the NSR and SR forms in patients with epilepsy and paid minor attention to the psychological characteristics of déjà vu experiences in patients with epilepsy and nonclinical individuals in this article. Psychological characteristics of these patients will be further analyzed in our next study.

In conclusion, patients with epilepsy could have two forms of déjà vu experiences (SR and NSR forms), although the NSR form was less common in patients with epilepsy than in nonclinical individuals. Despite several limitations, our results may contribute to the improvement of diagnostic reliability for patients with epilepsy with psychic experiences.

Conflict of interest statement

This study was done without any sponsorship. None of the authors report financial disclosures on this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2010.02.016.

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J Neurol
DOI 10.1007/s00415-011-6051-8

ORIGINAL COMMUNICATION

Clinical significance of periodic leg movements during sleep in rapid eye movement sleep behavior disorder

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Received: 15 March 2011 / Revised: 4 April 2011 / Accepted: 6 April 2011

Abstract The aim of the study was to explore the clinical significance of periodic leg movements during sleep (PLMS) in rapid eye movement sleep behavior disorder (RBD) and the pathological relation between these two disorders. Eighty-one consecutive idiopathic RBD (iRBD) patients, classified into two groups—27 patients with PLMS (iRBD–PLMS) and 54 patients without PLMS (iRBD w/o PLMS), and 31 patients with idiopathic PLMS (iPLMS)—were enrolled in this study. Descriptive variables including Epworth Sleepiness Scale (ESS) scores and polysomnography measures were compared among the three patient groups. Correlation analysis between the ratio of PLMS-related arousal index to PLMS index (PLMAI/PLMI) and sleep stage-related variables or clinically descriptive RBD variables was performed in the iRBD–PLMS group. Associated factors indicating the existence of PLMS during both stages NREM and REM were investigated in this group with clinically descriptive RBD variables. The iRBD–PLMS group showed a significantly lower ESS score and PLMAI/PLMI than the iPLMS group. The PLMAI/PLMI value negatively correlated with RWA/REM. RWA/REM was extracted as a factor that was significantly associated with the existence of PLMS during both stages NREM and REM. The RBD morbidity duration appeared as an associated factor for PLMS only during stage REM among the iRBD patients. In iRBD patients, daytime sleepiness remains modest probably because of suppressed cortical reactivity to PLMS. Increased PLMS activity during both stages NREM and REM is related to the mechanism of REM atonia loss caused by brainstem dysfunction. Especially, PLMS during stage REM might reflect the length of RBD morbidity.

Keywords REM sleep behavior disorder · REM sleep without atonia · Parasomnia · Periodic leg movements · Epworth Sleepiness Scale · α-Synucleinopathy

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Published online: 21 April 2011

Introduction

Rapid eye movement sleep behavior disorder (RBD) occurs idiopathically (iRBD) or secondarily to neurodegenerative diseases [23, 28] and frequently represents a prodromal phase of α-synucleinopathies [16, 26]. This important issue has recently encouraged many researchers to investigate predictive factors associated with development of α-synucleinopathies among iRBD patients [15, 25].

Periodic leg movements during sleep (PLMS) are extremely common among patients with restless legs syndrome (RLS) [22], and has been regarded to relate with dopaminergic dysfunction [21]. Furthermore, PLMS is frequently observed in patients with RBD [12, 23], suggesting that PLMS and RBD partly share a common pathogenesis: impairment of central dopaminergic transmission [12]. Some previous reports have suggested the