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.

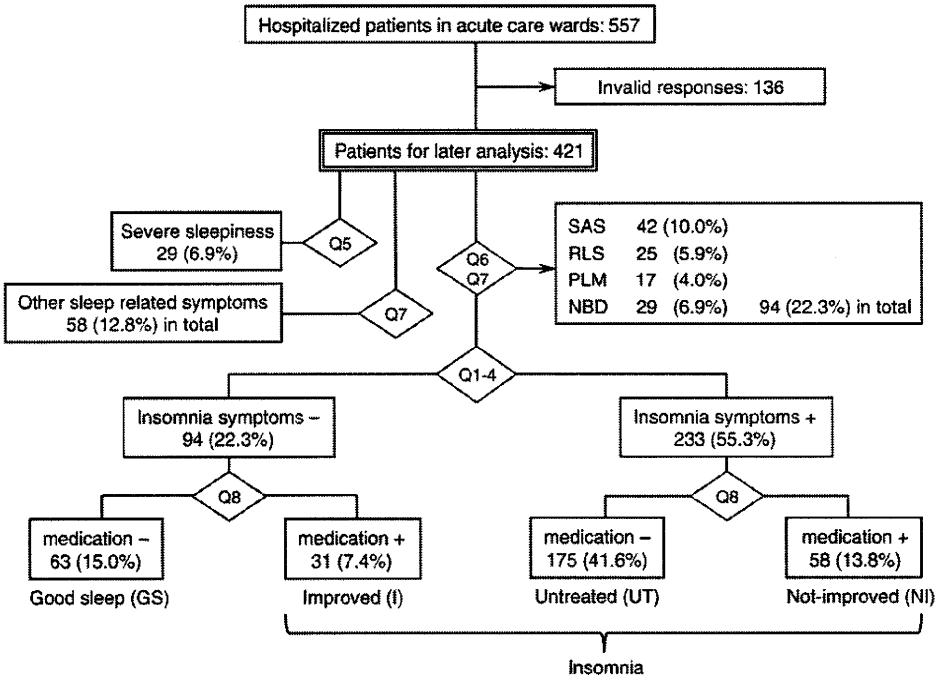

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

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.

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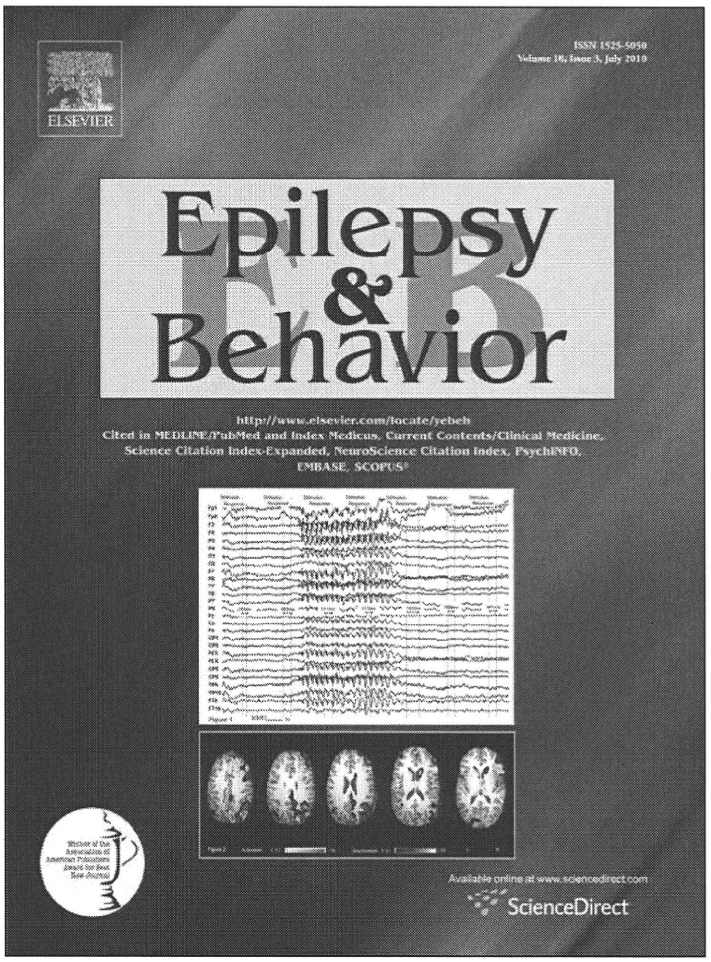
References

[1] Manabe K, Matsui T, Yamaya M, Sato-Nakagawa T, Okamura N, Arai H, et al. Sleep patterns and mortality among elderly patients in a geriatric hospital. Gerontology 2000;46:318–22.
[2] Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 2007;176:1299–304.
[3] Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257–62.
[4] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention. JAMA 1989;262:1479–84.
[5] Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. An epidemiological study of insomnia among the Japanese general population. Sleep 2000;23:41–7.
[6] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97–111.

[7] American Acdemy of SleepMedicine. International classification of sleep disorders :Diagnostic and coding manual. 2nd ed. Westchester: Illinois; 2005.
[8] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
[9] Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–9.
[10] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.
[11] Hui DS, Wong TY, Li TS, Ko FW, Choy DK, Szeto CC, et al. Prevalence of sleep disturbances in Chinese patients with end stage renal failure on maintenance hemodialysis. Med Sci Monit 2002;8:CR331–6.
[12] Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol 2001;18:128–47.
[13] Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord 2006;21:380–4.
[14] Hanly P, Powles P. Hypnotics should never be used in patients with sleep apnea. J Psychosom Res 1993;37(Suppl 1):59–65.
[15] Enomoto M, Eudo T, Suenaga K, Miura N, Nakano Y, Kohtoh S, et al. Newly developed waist actigraphy and its sleep/wake scoring algorithm. Sleep Biol Rhythms 2009;7:17–22.
[16] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.
[17] Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. J Psychosom Res 2009;67:109–16.
[18] Ulloa EW, Salup R, Patterson SG, Jacobsen PB. Relationship between hot flashes and distress in men receiving androgen deprivation therapy for prostate cancer. Psychooncology 2009;18:598–605.
[19] Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 1994;17:497–501.
[20] Stein MB, Chartier M, Walker JR. Sleep in nondepressed patients with panic disorder: I. Systematic assessment of subjective sleep quality and sleep disturbance. Sleep 1993;16:724–6.
[21] Partinen M. Epidemiology of sleep disorders. In: Kryger M, Roth T, Dement W, editors. Principals and oractice of sleep medicine. 2nd ed. Philadelphia: WB Saunders; 1994. p. 437–52.
[22] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
[23] Kim J, In K, You S, Kang K, Shim J, Lee S, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004;170:1108–13.
[24] The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
[25] Enomoto M, Li L, Aritake S, Nagase Y, Kaji T, Tagaya K, et al. Restless legs syndrome and its correlation with other sleep problems in the general population of Japan. Sleep Biol Rhythms 2006;4:153–9.
[26] Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006;35:350–64.
[27] Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004;56: 497–502.
[28] Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, et al. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep 2006;29: 1391–7.
[29] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. Sleep 2007;30:213–8.
[30] Meissner HH, Riemer A, Santiago SM, Stein M, Goldman MD, Williams AJ. Failure of physician documentation of sleep complaints in hospitalized patients. West J Med 1998;169:146–9.
[31] Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. Sleep 1999;22(Suppl 2):S359–65.
[32] Terzano MG, Parrino L, Cirignotta F, Ferini-Strambi L, Gigli G, Rudelli G, et al. Studio Morfeo: insomnia in primary care, a survey conducted on the Italian population. Sleep Med 2004;5: 67–75.
[33] Aikens JE, Rouse ME. Help-seeking for insomnia among adult patients in primary care. J Am Board Fam Pract 2005;18:257–61.
[34] Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. Pharmacoepidemiol Drug Saf 2002;11:97–104.
[35] Mahoney JE, Webb MJ, Gray SL. Zolpidem prescribing and adverse drug reactions in hospitalized general medicine patients at a Veterans Affairs hospital. Am J Geriatr Pharmacother 2004;2:66–74.
[36] Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005;331:1169.
[37] Chang CM, Wu EC, Chang S, Lin KM. Benzodiazepine and risk of hip fractures in older people: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 2008;16:686–92.



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Two forms of déjà vu experiences in patients with epilepsy

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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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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, $\kappa=0.400$–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	GE 4/49 : PE 71/263
	$X^2 = 4.57$/p = 0.032	$X^2 = 8.02$/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	L 23/103 : R 29/92 : Bil 23/114
	$X^2 = 3.24$/p = 0.137	$X^2 = 3.88$/p = 0.114
MTS in MRI studies (n = 309)	Exist 26/59 : Nil 146/250	Exist 19/59 : Nil 56/250
	$X^2 = 3.97$/p = 0.046	$X^2 = 3.88$/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 screlosis.

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.

References

[1] Adachi N, Koutroumanidis M, Elwes RDC, et al. Interictal ^{18}FDG PET findings in temporal lobe epilepsy with déjà vu. J Neuropsychiatry Clin Neurosci 1999;11:380–6.
[2] Cole M, Zangwill OL. Déjà vu in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1963;26:37–8.
[3] Bartolomei F, Barbeau E, Gavaret M, et al. Cortical stimulation study of the role of rhinal cortex in déjà vu and reminiscence of memories. Neurology 2004;63: 858–64.
[4] Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982;12:129–44.
[5] Halgren E, Walter RD, Cherlow DG, Crandall PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain 1978;101:83–117.
[6] Gastaut H. Dictionary of epilepsy: Part 1. Definitions. Geneva: World Health Organization; 1973.
[7] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489–501.
[8] Adachi T, Adachi N, Takekawa Y, et al. Déjà vu experiences in patients with schizophrenia. Compr Psychiatry 2006;47:389–93.
[9] Brauer R, Harrow M, Tucker GJ. Depersonalization phenomena in psychiatric patients. Br J Psychiatry 1970;117:509–15.
[10] Richardson TF, Winokur G. Déjà vu—as related to diagnostic categories in psychiatric and neurosurgical patients. J Nerv Ment Dis 1968;146:161–4.
[11] Harper MA. Déjà vu and depersonalisation in normal subjects. Aust NZ J Psychiatry 1969;3:67–74.
[12] Myers DH, Grant G. A study of depersonalization in students. Br J Psychiatry 1972;121:59–65.
[13] Palmer J. A community mail survey of psychic experiences. J Am Soc Psychical Res 1979;73:221–51.
[14] Adachi N, Adachi T, Kimura M, Akanuma N, Takekawa Y, Kato M. Demographic and psychological features of déjà vu experiences in a nonclinical Japanese population. J Nerv Ment Dis 2003;191:242–7.
[15] Brown AS. The déjà vu experience. New York: Psychology Press; 2004.
[16] Holmes MD, Dodrill CB. What is the significance of subjective events recorded during long-term EEG video monitoring? Epilepsia 1998;39:852–62.
[17] Silberman EK, Post RM, Nurnberger J, Theodore W, Boulenger JP. Transient sensory, cognitive and affective phenomena in affective illness. A comparison with complex partial epilepsy. Br J Psychiatry 1985;146:81–9.
[18] Neppe VM. The psychology of déjà vu: have I been here before? Johannesburg: Witwatersrand Univ. Press; 1983.
[19] Adachi N, Adachi T, Kimura M, Akanuma N, Kato M. Development of the Japanese version of the Inventory of Déjà vu Experiences Assessment (IDEA). Seishin Igaku 2001;43:1223–31 [In Japanese].
[20] Adachi N, Akanuma N, Adachi T, et al. Déjà vu experiences are rarely associated with pathological dissociation. J Nerv Ment Dis 2008;196:417–9.
[21] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[22] Adachi N, Alarcon G, Binnie CD, Elwes RDC, Polkey CE, Reynolds EH. Predictive value of interictal epileptiform discharges during non-REM sleep on scalp EEG recordings for lateralization of epileptogenesis. Epilepsia 1998;39:628–32.
[23] Adachi N, Kanemoto K, Muramatsu R, et al. Intellectual prognosis after status epilepticus in adult epilepsy patients: Analysis with Wechsler Adult Intelligence Scale—Revised. Epilepsia 2005;46:1502–9.
[24] Kanemoto K, Takeuchi J, Kawasaki J, Kawai I. Characteristics of temporal lobe epilepsy with medial temporal sclerosis, with special reference to psychotic episodes. Neurology 1996;47:1199–203.
[25] Sno HN, Schalken HFA, De Jonghe F, Koeter MWJ. The inventory for déjà vu experiences assessment: development, utility, reliability, and validity. J Nerv Ment Dis 1994;181:27–33.
[26] Neugebauer R. Reliability of seizure diaries in adult epileptic patients. Neuroepidemiology 1989;8:228–33.
[27] Erkwoh R, Steinmeyer EM. Phenomenology of simple partial seizures. Seizure 1996;5:283–9.
[28] Gupta A, Jeavons PM, Hughes RC, Covanis A. Aura in temporal lobe epilepsy: clinical and electroencephalographic correlation. J Neurol Neurosurg Psychiatry 1983;46:1079–80.
[29] Palmini A, Gloor P. The localizing value of auras in partial seizures: a prospective and retrospective study. Neurology 1992;42:801–8.
[30] Sno HN, Linszen DH. The déjà vu experience: remembrance of things past? Am J Psychiatry 1980;147:1587–95.
[31] Herper M, Roth M. Temporal lobe epilepsy and the phobic anxiety-depersonalization syndrome: Part 1. A comparative study. Compr Psychiatry 1962;3:129–51.
[32] Berkovic SF, Andermann F, Anderman E, Gloor P. Concepts of absence epilepsies: discrete syndromes or biological continuum? Neurology 1987;37:993–1000.
[33] Meencke HJ, Janz D. Neuropathological findings in primary generalized epilepsy: a study of eight cases. Epilepsia 1984;25:8–21.
[34] van Paesschen W, King MD, Duncan JS, Connelly A. The amygdala and temporal lobe simple partial seizures: a prospective quantitative MRI study. Epilepsia 2001;42:857–62.
[35] Bancaud J, Brunet-Bourgin F, Chauvel P, Halgren E. Anatomical origin of déjà vu and vivid 'memories' in human temporal lobe epilepsy. Brain 1994;117:71–90.
[36] Spatt J. Déjà vu: possible parahippocampal mechanisms. J Neuropsychiatr Clin Neurosci 2002;14:6–10.
[37] Devinsky O, Kelly K, Porter R, Theodore WH. Clinical and electrographic features of simple partial seizures. Neurology 1988;38:1347–52.
[38] Lieb JP, Walsh GZO, Babb TL, Walter RD, Crandall PH. A comparison of EEG seizure patterns recorded with surface and depth electrodes in patients with temporal lobe epilepsy. Epilepsia 1976;17:137–60.

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ORIGINAL COMMUNICATION

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

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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

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

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possibility of dysfunction of the nigrostriatal dopaminergic system as an important cause of RBD [5, 11, 29]. However, the results of neuropathological studies of the relation between the presence of RBD and dopaminergic dysfunction remain controversial [7, 8, 18].

The characteristics of PLMS in RBD patients have been compared to those in RLS patients [12, 20]. Nevertheless, to our knowledge, the clinical significance and underlying mechanism of the presence of PLMS in iRBD have not been conclusive. To clarify these issues, we investigated the influence of PLMS on subjective daytime sleepiness and the relation between clinical RBD variables and PLMS in patients with iRBD.

Methods

The Ethical Committee of the Neuropsychiatric Research Institute approved this retrospective study; informed consent was obtained from all participants. From consecutive patients who visited the outpatient clinic of the Japan Somnology Center during May 2003–August 2008, we enrolled 81 patients with iRBD and 31 patients with PLMS not showing symptoms suggesting RBD for this study (PLMS group). Diagnoses were made by at least two sleep-disorder expert physicians based on results of both nocturnal polysomnography (n-PSG) findings and clinical interviews according to the International Classification of Sleep Disorders, 2nd edition (ICSD-2) [4]. PLMS was found incidentally in the patients of the PLMS group, who had the following subjective complaints at their first visit: excessive daytime sleepiness ($n = 11$), habitual snoring ($n = 13$), and difficulty in initiating maintenance of sleep ($n = 7$). The enrolled patients took no medication both at the first visit and at the time of n-PSG, and had no symptom indicating the possible existence of RLS or any dementia. None had any abnormal neurological finding. For the apnea–hypopnea index on n-PSG, none showed 15 or more per hour. Patients with iRBD were classified into two groups: patients with PLMS index $\geq$15 events/hour [4] (iRBD–PLMS) and those without (iRBD w/o PLMS).

For iRBD groups with and without PLMS, and the PLMS group, we compared diagnostic n-PSG variables and the Epworth Sleepiness Scale (ESS) [17] scores at the first visit to the clinic. Among the n-PSG variables, we specifically calculated the common PLMS-related variables including PLMS index, mean duration of PLMS, and the inter-PLMS interval for stage NREM and for stage REM including stage REM without atonia (RWA) [20]. These variables were compared between the iRBD–PLMS group and the PLMS group.

For iRBD patients, clinically descriptive RBD variables were evaluated, including the duration of RBD morbidity reported by patients themselves or their bed partners, proportion of stage RWA—an important physiological background of RBD [10]—to total stage REM (RWA/REM), and severity of RBD symptoms. As in a prior study [30], the iRBD severity was classified mainly based on the frequency of dream enactment behavior according to the revised ICSD [3].

Especially in the iRBD–PLMS group, correlation between the ratio of the number of PLMS-related arousal to the total number of PLMS and the n-PSG variables was investigated in addition to the clinically descriptive RBD variables. Moreover, for all enrolled iRBD patients, we investigated the associated factors for the existence of PLMS during both stage NREM and REM among the demographic variables and the clinically descriptive RBD variables indicated above.

Nocturnal polysomnography

Using a standard system (Alice 5; Respironics Inc., Murrysville, PA, USA) with video monitoring of patient behavior, diagnostic n-PSG recordings and measurements including four channels of the scalp EEG (C3/A2, C4/A1, O1/A2, O2/A1), two electrooculograms (EOG), submental electromyogram (EMG), electrocardiogram, nasal/oral airflow, oximetry sensor for SpO_2 recording, a microphone for snoring sounds, chest/abdominal respiratory effort, and anterior tibialis electromyogram for leg movements (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of right and left legs) were taken.

Scoring of PSG measures

Sleep stages were scored according to the criteria set by Rechtschaffen and Kales [27]. Since RBD patients lack muscle atonia, REM sleep was scored without submental EMG atonia. The onset and the termination of REM sleep were determined according to the method of Lapierre et al. [19]. EEG arousal was evaluated according to the criteria set by the American Sleep Disorders Association [6]. Respiratory events were assessed according to the diagnostic criteria of the American Academy of Sleep Medicine Task Force [1]. As described in earlier reports [10, 19], RWA was scored based on the following criteria: (1) tonic REM sleep—submentalis muscle EMG activity was present for more than 50% of a 30-s epoch; (2) phasic REM sleep—3-s epoch showing bursts of EMG activity of the submentalis muscle and anterior tibialis muscle, with an amplitude that is at least four times greater than that of background EMG, and 0.1–5.0 s in duration. Then PLMS was scored according to criteria set by the American Academy of Sleep Medicine [2]. PLMS were carefully

distinguished from phasic EMG activity on anterior tibialis muscle during stage REM in the anterior tibialis based upon their regular periodicity [14].

Statistical analyses

The chi-square test followed by residual analysis was used to compare the differences in gender distribution among the groups of iRBD w/o PLMS, iRBD-PLMS, and PLMS. Comparisons of age and ESS scores among the three groups were conducted using a Kruskal–Wallis test followed by Mann–Whitney's U test with Bonferroni correction as post hoc analysis. The estimated duration of RBD morbidity, RWA/REM, and the PLMS-related variables during stage REM were compared between the iRBD groups with and without PLMS using Mann–Whitney's U test. Regarding PLMS-related variables during stage NREM and the other polysomnographic variables, comparisons were made among the iRBD–PLMS group, the iRBD w/o PLMS group, and the PLMS group using a Kruskal–Wallis test followed by a Mann–Whitney's U test with Bonferroni correction as post hoc analysis. Moreover, in the group with iRBD–PLMS and that with PLMS, the PLMS-related variables during stage NREM and stage REM were compared using Wilcoxon's signed rank test.

In the iRBD–PLMS patients, correlation was calculated between the ratio of the number of PLMS-related arousal to the total number of PLMS and the n-PSG measures including PLMS-related variables or clinically descriptive RBD variables using Spearman's rank correlation coefficient. The associated factors for the existence of PLMS during both stage NREM and stage REM were also investigated using univariate and multivariate logistic regression analyses with the clinically descriptive RBD variables and demographic variables described above as independent variables among all subject iRBD patients.

Results

Demographic characteristics, ESS scores, and clinically descriptive variables of subject patient groups

As shown in Table 1, a significant difference was found among the ESS scores of the three patient groups ($H = 9.969$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the scores in the group with iRBD w/o PLMS ($p < 0.01$) and those in the group with iRBD–PLMS were significantly lower than those in PLMS ($p < 0.05$), but no significant difference was found between the former two groups. Among the clinically descriptive RBD variables, neither the severity of iRBD nor the estimated duration of RBD morbidity showed significant differences between the two iRBD groups.

Comparison of polysomnographic variables among the groups of iRBD-PLMS, iRBD w/o PLMS, and PLMS

As shown in Table 2, the RWA/REM in the iRBD–PLMS group was significantly higher than that in the iRBD w/o PLMS group ($U = 399.0$, $p < 0.01$). The proportions of stage-atonic REM were significantly different among the three patient groups ($H = 12.115$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the iRBD–PLMS group showed a significantly lower proportion of stage-atonic REM than either the iRBD w/o PLMS group or the PLMS group did ($p < 0.01$ respectively). The proportions of total stage

Table 1 Demographic characteristics, scores of ESS, and clinical descriptive RBD variables of subjects

	Total with iRBD	iRBD w/o PLMS	iRBD–PLMS	PLMS
No. of subjects	81	54 (68.6)	27 (31.4)	31
Sex (M:F)	52:29	37:17	15:12	19:12
Age, years	66.5 ± 7.0	65.9 ± 6.9	67.7 ± 7.1	63.5 ± 5.9
Score of ESS	6.0 ± 4.3	6.0 ± 4.2**	6.5 ± 4.7*	9.3 ± 5.3
Severity of iRBD[a]	2.6 ± 0.7	2.6 ± 0.7	2.5 ± 0.6	0
Estimated duration of iRBD, years	4.5 ± 3.3	4.0 ± 2.6	5.5 ± 6.2	0

Parenthesis indicates percentage of patients with or without PLMS in total iRBD patients

PLMS periodic leg movements during sleep, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *iRBD w/o PLMS* iRBD without PLMS, *iRBD–PLMS* iRBD with PLMS

* $p < 0.05$, ** $p < 0.01$, compared to the PLMS group

[a] Severity of iRBD was scored according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

Table 2 Comparison of polysomnograhic variables among iRBD with and without PLMS, and PLMS

	iRBD w/o PLMS ($n = 54$)	iRBD–PLMS ($n = 27$)	PLMS ($n = 31$)
PSG measures			
Sleep efficiency, %	85.2 ± 9.6	83.7 ± 9.2	82.5 ± 10.9
Stage 1, %SPT	10.0 ± 8.4	8.1 ± 4.1	7.2 ± 4.1
Stage 2, %SPT	54.3 ± 9.1	52.2 ± 9.0	54.9 ± 10.1
Stage 3 + 4, %SPT	4.5 ± 6.0	4.2 ± 4.8	5.6 ± 5.0
Stage atonic REM, %SPT	16.3 ± 6.0	12.0 ± 6.2**[a],**[b]	14.7 ± 6.8
Stage RWA, %SPT	5.5 ± 4.4	7.2 ± 4.8	0.0
Stage RWA, %REM	19.7 ± 19.7	36.5 ± 19.4**[a]	0.0
PLMS index, events/h[e]	3.0 ± 4.3	54.2 ± 27.4**[a]	47.7 ± 23.9**[a]
Ratio of PLMS related arousal to PLMS%[d,e]	7.1 ± 7.0*[b]	8.2 ± 4.4*[b]	16.6 ± 16.5
Index, duration and interval of PLMS during stage NREM[e]			
PLMS index, events/h	2.4 ± 3.4	53.9 ± 30.1*[a]	53.8 ± 23.9*[a]
Mean duration of PLMS, s	1.9 ± 0.4	1.8 ± 0.6	1.9 ± 0.6
Inter-PLMS interval, s	29.4 ± 3.1	29.0 ± 4.7	31.5 ± 5.7
Index, duration and interval of PLMS during stage REM[f]			
PLMS index, events/h	–	47.0 ± 33.8**[b]	10.3 ± 32.6*[c]
Mean duration of PLMS, s	–	2.6 ± 0.9**[b],*[c]	1.5 ± 0.9[c]
Inter-PLMS interval, s	–	28.2 ± 4.8**[b]	37.9 ± 7.8*[c]

PSG polysomnography, *SPT* sleep period time, *REM* rapid eye movement, *RWA* REM sleep without atonia; *PLMS* periodic leg movements during sleep, *NREM* non REM, *iRBD–PLMS* idiopathic rapid eye movement sleep behavior disorder with PLMS

* $p < 0.05$, ** $p < 0.01$

[a] Compared to iRBD w/o PLMS group

[b] Compared to PLMS group

[c] Compared to stage NREM. Values are expressed as mean ± SD

[d] PLMS related arousal index/PLMS index

[e] $n = 25$ in the iRBD w/o PLMS group

[f] $n = 18$ in the PLMS group

REM were also significantly different among the three patient groups ($H = 18.803$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the compared to the PLMS group, the iRBD–PLMS group and the iRBD without PLMS group showed a significantly higher proportion of total stage REM ($p < 0.05$ and $p < 0.01$, respectively).

As for PLMS-related variables, significant differences were found in the PLMS index ($H = 84.938$, $df = 2$, $p < 0.01$) and the ratio of PLMS-related arousal to PLMS ($H = 9.545$, $df = 2$, $p < 0.01$) among the three patient groups during the total sleep period. No significant difference in the PLMS index was observed between the iRBD–PLMS group and the PLMS group. With respect to the ratio of PLMS-related arousal to PLMS, the iRBD–PLMS group and the iRBD w/o PLMS group showed a significantly lower value than the PLMS group did ($p < 0.05$, respectively). No significant difference in the ratio was observed between the iRBD–PLMS group and the iRBD w/o PLMS group.

During stage NREM, there were significant differences in the PLMS index ($H = 84.552$, $df = 2$, $p < 0.01$) among the three patient groups. Post hoc tests revealed that the iRBD–PLMS group and the PLMS group each showed a significantly higher PLMS index than the iRBD w/o PLMS group did ($p < 0.01$). However, no significant difference in the index was observed between the iRBD–PLMS group and the PLMS group. Moreover, no significant difference in either the duration or the interval of PLMS was observed among the three patient groups.

During stage REM, the iRBD–PLMS group showed a significantly higher PLMS index than the PLMS group did ($U = 67.0$, $p < 0.01$). Furthermore, the PLMS duration was significantly longer ($U = 58.5$, $p < 0.01$) and the interval of PLMS was significantly shorter in the iRBD–PLMS group ($U = 58.5$, $p < 0.01$) than in the PLMS group ($U = 57.5$, $p < 0.01$).

In the PLMS group, the PLMS index was significantly higher ($Z = -3.978$, $p < 0.05$), the duration of PLMS was significantly longer ($Z = -2.592$, $p < 0.05$), and the inter-PLMS interval was significantly shorter ($Z = -1.940$, $p < 0.05$) during stage NREM than during stage REM. However, in the iRBD–PLMS group, only the PLMS

duration was significantly longer during stage REM than during stage NREM ($Z = -3.697$, $p < 0.01$).

Factors correlated with the ratio of the number of PLMS-related arousals to the total number of PLMS in each sleep stage

To clarify the mechanism of low ratio of PLMS-related arousal to the total number of PLMS, we conducted correlation analyses between the ratio and either the n-PSG variables or clinically descriptive RBD variables. In the iRBD−PLMS group, among the studied variables, only RWA/REM showed significant and negative correlation with the ratio ($r_s = -0.375$, $p < 0.05$) (Fig. 1).

Factors associated with the existence of PLMS during stage NREM in iRBD patients

Among all iRBD patients, 27 patients (31.4%) who showed a PLMS index of more than 15 events/h during stage NREM were designated as the group with the existence of PLMS during stage NREM (mean PLMS index during NREM [SD]; 53.9 [30.0] in iRBD-PLMS, 2.4 [3.4] in iRBD w/o PLMS).

Univariate logistic regression analyses were performed to ascertain the associated factor for the existence of PLMS during stage NREM with the following five independent variables: gender, age, severity of iRBD, estimated duration of RBD morbidity, and RWA/REM. Among these variables, RWA/REM was significantly associated with the existence of PLMS during stage NREM in the univariate model (10% increase in RWA/REM: OR = 1.42, 95%CI 1.12–1.81). Multivariate logistic regression analysis also revealed that the existence of PLMS during this sleep stage was significantly associated only with a 10% increase in RWA/REM (OR = 1.45, 95%CI 1.12–1.89) (Table 3).

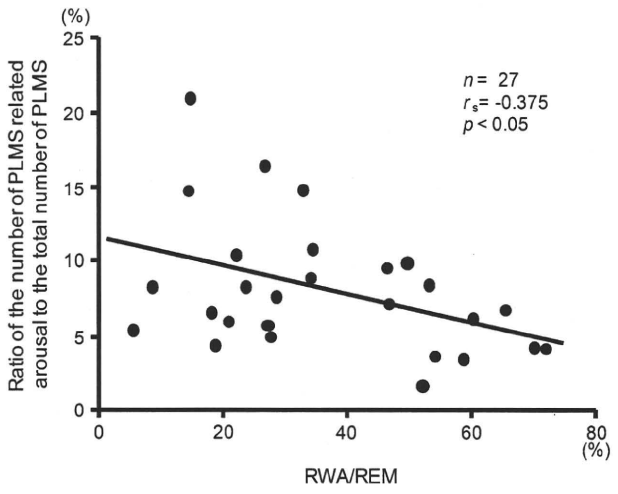

Fig. 1 Correlation between RWA/REM and ratio of PLMS-related arousal index to PLMS index in patients with iRBD-PLMS. *PLMS* periodic leg movement during sleep, *REM* rapid eye movement, *iRBD–PLMS* idiopathic rapid eye movement sleep behavior disorder with PLMS, *RWA/REM* proportion of stage REM without atonia to total stage REM (atonic REM and RWA)

Factors associated with the existence of PLMS during stage REM in iRBD patients

Twenty-five patients (30.9%) who showed a PLMS index of more than 15 events/h during stage REM were designated as the group with the existence of PLMS during stage REM (mean PLMS index during REM [SD]; 47.0 [33.8] in iRBD-PLMS, 0.1 [0.6] in iRBD w/o PLMS).

Univariate logistic regression analyses were performed to ascertain the factors associated with the existence of PLMS during stage REM with the five independent variables indicated above. Among these variables, two items (estimated duration of RBD morbidity and RWA/REM) were significantly associated with the existence of PLMS during stage REM in the univariate model (estimated duration of RBD morbidity: OR = 1.18, 95%CI 1.01–1.38, 10% increase in RWA/REM: OR = 1.44, 95%CI 1.13–1.83). Multivariate logistic regression analysis also revealed that the existence of PLMS during stage REM was significantly associated with the estimated duration of RBD morbidity (OR = 1.19, 95%CI 1.00–1.41) and a 10% increase in RWA/REM (OR = 1.45, 95%CI 1.11–1.88) (Table 4).

Discussion

This is the first study to elucidate both the influence of PLMS on the level of subjective daytime sleepiness manifested on ESS in patients with iRBD and the relation between PLMS measures and clinical iRBD variables. Reportedly, the existence of PLMS contributes to the occurrence of excessive daytime sleepiness [24]. However, the ESS score in the iRBD–PLMS group was remarkably lower than the value in the PLMS group despite a similar value of PLMS index between these two groups. The value in the iRBD–PLMS group was similar to that in the iRBD w/o PLMS group. Moreover, the iRBD–PLMS group showed a significantly lower ratio of PLMS-related arousal index to the total PLMS index than the PLMS group did, which is quite compatible with the report by Fantini et al., in which RBD patients had smaller EEG activation associated with PLMS than in RLS patients [12].

In the present study, the two iRBD groups showed a higher proportion of stage REM than the PLMS group, and the iRBD–PLMS group showed a higher proportion of RWA to total stage REM than the PLMS group. The reason

Table 3 Factors associated with the existence of PLMS during stage NREM in iRBD patients

Predictor	Total	PLMS index during stage NREM ≥ 15 events/h		Univariate model	*p*	Multivariate model	*p*
	n	*n*	%	Odds ratio (95%CI)		Adjusted odds ratio (95%CI)	
Gender							
Female	29	12	41.3	1.00 (ref)			
Male	52	15	28.8	0.57 (0.22–1.49)	0.25		
Age, years	81			1.74 (0.67–1.51)	0.25		
Severity of RBD[a]							
Mild	7	2	28.6	1.00 (ref)			
Moderate	21	9	42.9	1.88 (0.29–11.97)	0.51		
Severe	53	16	30.2	1.08 (0.19–6.17)	0.93		
Duration of RBD, years	81			1.15 (0.99–1.33)	0.07		
RWA/REM, 10%[b]	81			1.42 (1.12–1.81)	<0.01	1.45 (1.12–1.89)	<0.01

CI confidence interval, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *PLMS* periodic leg movements during sleep, *RWA* rapid eye movement sleep without atonia, *NREM* non rapid eye movement, *RWA/REM* proportion of stage RWA to total stage REM (atonic REM and RWA)

[a] Severity of RBD was classified according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

[b] Odds ratio was expressed as the ratio for 10% increase in RWA/REM

Table 4 Factors associated with the existence of PLMS during stage REM in iRBD patients

Predictor	Total	PLMS index during stage NREM ≥ 15 events/h		Univariate model	*p*	Multivariate model	*p*
	n	*n*	%	Odds ratio (95%CI)		Adjusted odds ratio (95%CI)	
Gender							
Female	29	11	37.9	1.00 (ref)			
Male	52	14	26.9	0.60 (0.23–1.59)	0.31		
Age, years	81			1.04 (0.97–1.12)	0.25		
Severity of RBD[a]							
Mild	7	1	14.3	1.00 (ref)			
Moderate	21	9	42.9	4.50 (0.46–14.29)	0.20		
Severe	53	15	28.3	2.37 (0.26–21.37)	0.44		
Duration of RBD, years	81			1.18 (1.01–1.38)	<0.05	1.19 (1.00–1.41)	<0.05
RWA/REM, 10%[b]	81			1.44 (1.13–1.83)	<0.01	1.45 (1.11–1.88)	<0.01

CI confidence interval, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *PLMS* periodic leg movements during sleep, *REM* rapid eye movement, *RWA* REM sleep without atonia, *RWA/REM* proportion of stage RWA to total stage REM (atonic REM and RWA)

[a] Severity of RBD was classified according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

[b] Odds ratio was expressed as the ratio for 10% increase in RWA/REM

for the higher proportion of stage REM in iRBD patients was unclear; however, this finding was consistent with that of a previous study in which a trend toward an increased REM sleep percentage was found among RBD patients [13]. It is particularly interesting that the increased amount of RWA was proven to be associated with the lower arousal response to PLMS in the iRBD–PLMS group, although the negative correlation between these two variables was considered to be weak. Considering those facts, it is possible that the impairment of cortical reactivity to

PLMS becomes more pronounced along with the progression of RWA in patients with iRBD, probably engendering the absence of daytime sleepiness in this patient group.

Comparison of PLMS-related variables in stage NREM and stage REM revealed that the PLMS group had higher activity of PLMS manifested as the significantly higher PLMS index, shorter inter-PLMS interval, and longer mean duration of PLMS in stage NREM than in stage REM, which is consistent with results of previous studies of RLS patients [12, 20]. The characteristics of PLMS in the iRBD–PLMS group differed from those in the PLMS group in that the PLMS index and the inter-PLMS interval did not differ between stages REM and NREM; the mean duration of PLMS during stage REM was longer than that during stage NREM in this group. As Fantini et al. [12] reported, increased activity of PLMS during stage REM could arise from the disinhibition of motor control during this sleep stage associated with the disorder. The disinhibition explains the high PLMS index during stage REM in the iRBD group. However, considering the longer duration and the shorter interval of PLMS during stage REM, the PLMS rhythm formation process occurring during this sleep stage in the iRBD patient group might be associated not only with the disinhibition of motor control, but also with other RBD-associated mechanisms.

The most noteworthy finding in this study was that a 10% increase in the proportion of stage RWA to stage REM was revealed to be associated with the existence of PLMS during both stage REM and stage NREM among the subject iRBD patients. In addition, the estimated duration of iRBD morbidity was associated with the existence of PLMS only during stage REM. In summary, in iRBD patients, the process of RWA formation was thought to be associated with the process of PLMS formation during both stage NREM and stage REM. Moreover, given the relation to the length of morbidity of RBD, the mechanism of PLMS—especially during stage REM—might be reflected in the RBD disease process.

This study has some limitations. First, daytime sleepiness was evaluated only with the self-checked ESS score, but not with multiple sleep latency test, an objective measure for daytime sleepiness [9]. Future studies should objectively evaluate the influence of PLMS on daytime sleepiness in patients with RBD. Second, the present study was conducted with the retrospective design. Iranzo et al. [15] reported that excessive EMG activity increases with time course suggesting a progressive dysfunction of brainstem structures that modulate REM sleep atonia in idiopathic RBD. Further study would be necessary to investigate the changes in the amount of PLMS prospectively to support the possibility of the presence of PLMS as a biological marker of RBD. Third, the PLMS group did not consist of homogenous subjects, e.g. PLM disorder and incidental PLMS found in sleep onset insomnia and habitual snorer.

In conclusion, the influence of PLMS on daytime sleepiness is modest in iRBD patients, probably because of the impaired cortical reactivity to PLMS. In iRBD patients, PLMS occurs more frequently during stage REM. Disinhibition of motor control in stage REM underlying the process of RWA formation might be related with the presence of PLMS not only during stage REM but also during stage NREM. Moreover, PLMS especially during stage REM might reflect the length of RBD morbidity, probably related to the RBD disease process.

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Conflict of interest None.

References

1. AASM: American Academy of Sleep Medicine Task Force (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep 22:667–689
2. AASM: American Academy of Sleep Medicine (2007) The AASM manual for the scoring of sleep and associated events: rules. Terminology and Technical Specifications, Westchester
3. AASM (2001) International classification of sleep disorders: diagnostic and coding manual revised. American Academy of Sleep Medicine, Westchester
4. AASM (2005) International classification of sleep disorders: diagnostic and coding manual, 2nd ed. American Academy of Sleep Medicine, Westchester
5. Albin RL, Koeppe RA, Chervin RD, Consens FB, Wernette K, Frey KA, Aldrich MS (2000) Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology 55:1410–1412
6. ASDA: American Sleep Disorders Association Task Force (1992) EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 15:173–184
7. Boeve BF, Dickson DW, Olson EJ, Shepard JW, Silber MH, Ferman TJ, Ahlskog JE, Benarroch EE (2007) Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. Sleep Med 8:60–64
8. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, Benarroch EE, Ahlskog JE, Smith GE, Caselli RC, Tippman-Peikert M, Olson EJ, Lin SC, Young T, Wszolek Z, Schenck CH, Mahowald MW, Castillo PR, Del Tredici K, Braak H (2007) Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 130:2770–2788
9. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S (1986) Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 9:519–524
10. Consens FB, Chervin RD, Koeppe RA, Little R, Liu S, Junck L, Angell K, Heumann M, Gilman S (2005) Validation of a polysomnographic score for REM sleep behavior disorder. Sleep 28:993–997

11. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K (2000) Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. Brain 123(Pt 6):1155–1160
12. Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J (2002) Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology 59:1889–1894
13. Ferini-Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF (2004) Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): does the idiopathic form of RBD really exist? Neurology 62:41–45
14. Frauscher B, Iranzo A, Hogl B, Casanova-Molla J, Salamero M, Gschliesser V, Tolosa E, Poewe W, Santamaria J (2008) Quantification of electromyographic activity during REM sleep in multiple muscles in REM sleep behavior disorder. Sleep 31:724–731
15. Iranzo A, Luca Ratti P, Casanova-Molla J, Serradell M, Vilaseca I, Santamaria J (2009) Excessive muscle activity increases over time in idiopathic REM sleep behavior disorder. Sleep 32:1149–1153
16. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, Tolosa E (2006) Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 5:572–577
17. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14:540–545
18. Kim YK, Yoon IY, Kim JM, Jeong SH, Kim KW, Shin YK, Kim BS, Kim SE (2010) The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. Eur J Neurol 17:487–492
19. Lapierre O, Montplaisir J (1992) Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 42:1371–1374
20. Manconi M, Ferri R, Zucconi M, Fantini ML, Plazzi G, Ferini-Strambi L (2007) Time structure analysis of leg movements during sleep in REM sleep behavior disorder. Sleep 30:1779–1785
21. Manconi M, Ferri R, Zucconi M, Oldani A, Fantini ML, Castronovo V, Ferini-Strambi L (2007) First night efficacy of pramipexole in restless legs syndrome and periodic leg movements. Sleep Med 8:491–497
22. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P (1997) Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 12:61–65
23. Olson EJ, Boeve BF, Silber MH (2000) Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 123(Pt 2):331–339
24. Pallesen S, Nordhus IH, Omvik S, Sivertsen B, Tell GS, Bjorvatn B (2007) Prevalence and risk factors of subjective sleepiness in the general adult population. Sleep 30:619–624
25. Postuma RB, Gagnon JF, Rompre S, Montplaisir JY (2010) Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 74:239–244
26. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY (2009) Idiopathic REM sleep behavior disorder in the transition to degenerative disease. Mov Disord 24:2225–2232
27. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages in human subjects. US Government Printing Office, Washington DC
28. Schenck CH, Mahowald MW (2002) REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 25:120–138
29. Uchiyama M, Isse K, Tanaka K, Yokota N, Hamamoto M, Aida S, Ito Y, Yoshimura M, Okawa M (1995) Incidental Lewy body disease in a patient with REM sleep behavior disorder. Neurology 45:709–712
30. Yamamoto K, Uchimura N, Habukawa M, Takeuchi N, Oshima H, Oshima M, Maeda H (2006) Evaluation of the effects of paroxetine in the treatment of REM sleep behavior disorder. Sleep Biol Rhythms 4:190–192