sary amendments made. After trial use of the amended questionnaire in a cohort of Japanese RLS patients, version 2 was prepared. Version 2 was similarly back-translated into English, and after confirming that no translation-related issues remained, the draft version was finalized and used in the present study.

The J-IRLS scale consists of the same 10 items (questions) as the English version. Each item has a set of five response options graded from no RLS or impact (score = 0) to very severe RLS or impact (score = 4), and is scored by individual patients. The scores of all 10 items are added together to give a total score ranging from 0 to 40.

Study design

Patients who proceeded to the screening phase included 34 de novo patients and 25 patients on existing treatment. The patients already on treatment continuously received the treatment during the screening phase. These latter 25 patients included six symptom-free patients and seven borderline patients (Table 1). However, prior to implementation of this study it had been confirmed by a physician that their symptoms clearly met the IRLSSG diagnostic criteria. Although the 25 patients already on treatment continuously received the treatment during the screening phase, the medications were washed out prior to entering the treatment phase of the present study. These medications included levodopa or dopamine agonists ($n = 13$), clonazepam ($n = 3$), and others ($n = 9$). At the first visit, each patient self-assessed his or her RLS symptoms by J-IRLS under a physician's supervision then underwent assessment of CGI-Severity of Illness (CGI-S) by another physician. Two weeks afterwards at the second visit, J-IRLS and CGI-S were reevaluated in the same manner.

Observation of changes in RLS symptoms was made from baseline to 6 weeks after entering this double-blind, placebo-controlled trial. PGI was assessed by patients themselves and CGI-I by physicians during the treatment period. PSQI-J[13] was self-assessed by patients both at baseline and at 6 weeks after administration.

Statistical analysis

Reliability of J-IRLS was evaluated by a test–retest reliability analysis of both IRLS total score and scores of the 10 items of the scale. The results were assessed by intra-class correlation coefficient (ICC) and linear weighted Kappa statistics, respectively.

The validity analyses consisted of estimation of both internal consistency and concurrent validity in the 59 subjects who entered the screening phase of the main study. In order to confirm one domain structure of J-IRLS, we examined the internal consistency of the 10 items of IRLS. Internal consistency was assessed by Cronbach's alpha calculated for the 10 items whereas concurrent validity was assessed by correlation coefficient of the J-IRLS total score with CGI-S score. The factor structure of J-IRLS 10 items was explored using the principal factor analysis with oblique promax rotation on the 56 subjects who entered the treatment period. The number of factors in this analysis was evaluated by scree plot of eigenvalue. To explore the correlation between J-IRLS and PSQI-J, the factor structure of J-IRLS 10 items and PSQI-J items was extracted by performing principal factor analysis.

According to the previous study reported by Abetz *et al.*,[8] we compared the effect size used as a measure of the change in J-IRLS scores with CGI-I or PGI to evaluate the responsiveness of the J-IRLS to pramipexole treatment. Responsiveness of the J-IRLS to pramipexole treatment was investigated in 37 patients who completed the 6 weeks' observation by evaluation of the correlations between change of J-IRLS total score over 6 weeks' treatment with pramipexole and CGI-I and PGI. Moreover, change of J-IRLS total score was compared among subgroups on CGI-I and PGI by Kruskal–Wallis test. CGI-I categories were grouped into 'very much improved', 'much improved', 'essentially stable', and 'worsened'. Meanwhile, PGI categories were grouped into 'very much better', 'much better', 'essentially stable', and 'worsened' because the number of patients with CGI-I item scores of 'minimally worsened', 'much worse', and 'very much worse', and PGI item scores of 'a little worse', 'much worse', and 'very much worse' was too small to calculate effect sizes. Therefore, 'essentially stable' on CGI included 'minimally improved', 'no change', and 'minimally worsened' while 'essentially stable' on PGI included 'a little better', 'no change', and 'a little worse'. On both rating scales, 'worsened' included 'much worse' and 'very much worse'. Effect sizes were calculated by dividing the change of mean J-IRLS total scores from baseline by the SD of mean scores at baseline.

Significance level in this study was set at 0.05 with two-tailed, and 95% confidence interval (CI) was

calculated. All statistical analyses were conducted using SAS ver.8.02 (SAS Institute, Cary, NC, USA).

RESULTS

Test–retest reliability

J-IRLS total score in the 59 patients was 19.5 ± 9.3 (mean ± SD) at the first visit and 19.2 ± 9.5 at the second visit. ICC was 0.877 (95%CI, 0.802–0.925). Percentages of complete agreement for J-IRLS 10 items between test and retest and linear-weighted Kappa statistics are shown in Table 2. The proportion of complete agreement ranged from 49.2 to 71.2%. Linear-weighted Kappa statistics ranged from 0.493 (question 3, relief of symptom while moving around) to 0.745 (question 7, frequency of RLS symptoms).

Validity analysis

Internal consistency

Cronbach's alpha coefficient among the 10 items of J-IRLS was 0.942 ($n = 59$) for the first visit and 0.954 ($n = 59$) for the second visit during screening.

Concurrent validity

Among 59 patients, Pearson's correlation coefficient of J-IRLS total score and CGI-S score for the first and second visits was 0.804 and 0.796, respectively (both $P < 0.0001$).

Construct validity

Factor analysis on J-IRLS 10 items

Eigenvalues for the first visit during screening were 6.395 for the first factor and 0.691 for the second factor. At the second visit, the values were 6.942 and 0.552, respectively. Scree plots of eigenvalues showed a clear break at the third factor. Therefore, we accepted a two-factor solution, which accounted for 95.3% and 97.0% of the variance for each visit. Eight of the items differentially loaded onto these two factors in both visits (Table 3). Five items (items 1, 2, 3, 7, and 8) could be included in the first factor, each with loadings of >0.57 on the first factor and <0.26 on the second factor. Three items (items 5, 9, and 10) loaded >0.62 on the second factor and <0.24 on the first factor. The two remaining items (items 4 and 6) loaded about equally on both factors. The values for ICC for the first factor (total score of items 1, 2, 3, 7, and 8) and the second factor (total score of items 5, 9, and 10) were calculated to be 0.874 (95%CI, 0.796–0.923) and 0.810 (95%CI, 0.700–0.882), respectively.

Factor analysis of PSQI-J sub-items together with J-IRLS

In the 56 examined patients, the correlation coefficient between J-IRLS total score and PSQI-J was 0.495 ($P = 0.0001$).

A significant correlation was observed between subscales of PSQI-J and J-IRLS. PSQI-J sleep duration

Table 2. Percentage of complete agreement and weighted Kappa statistics for IRLS items

	IRLS items	*n*	Percentage of complete agreement (*n*)	Weighted Kappa statistics (95%CI)†
1	Discomfort in legs/arms	59	61.0 (36)	0.643 (0.504, 0.781)
2	Need to move	59	54.2 (32)	0.574 (0.432, 0.716)
3	Relief from moving around	59	49.2 (29)	0.493 (0.337, 0.650)
4	Sleep disturbance	59	54.2 (32)	0.590 (0.445, 0.734)
5	Tiredness/sleepiness	59	62.7 (37)	0.674 (0.556, 0.792)
6	Severity as a whole	59	71.2 (42)	0.721 (0.594, 0.848)
7	How often	59	71.2 (42)	0.745 (0.627, 0.863)
8	Average severity	59	59.3 (35)	0.613 (0.471, 0.754)
9	Impact on daily affairs	59	64.4 (38)	0.644 (0.500, 0.787)
10	Mood disturbance	59	54.2 (32)	0.530 (0.381, 0.678)

†Linear weighted Kappa statistics.
CI, confidence interval; IRLS, International Restless Legs Syndrome Study Group Rating Scale.

Table 3. Factor loadings on the IRLS items in two-factor model

		First visit			Second visit		
	J-IRLS	Factor1	Factor2	Communality	Factor1	Factor2	Communality
1	Discomfort in legs/arms	***0.875***	0.094	0.882	***0.824***	0.157	0.886
2	Need to move	***0.996***	−0.148	0.820	***0.869***	0.007	0.763
3	Relief from moving around	***0.702***	0.043	0.534	***0.847***	0.001	0.718
4	Sleep disturbance	0.505	0.444	0.747	0.326	0.628	0.789
5	Tiredness/sleepiness	−0.015	***0.764***	0.569	0.040	***0.818***	0.718
6	Severity as a whole	0.573	0.431	0.840	0.592	0.376	0.806
7	How often	***0.638***	0.260	0.692	***0.660***	0.233	0.709
8	Average severity	***0.577***	0.260	0.598	***0.648***	0.221	0.672
9	Impact on daily affairs	−0.028	***0.913***	0.801	0.008	***0.877***	0.780
10	Mood disturbance	0.207	***0.623***	0.601	0.236	***0.624***	0.653

Factor loading was calculated by principal factor analysis.
Factor loadings for the critical items are indicated in bold and italics.
IRLS, International Restless Legs Syndrome Study Group Rating Scale; J-IRLS, the Japanese version of IRLS.

showed a weak but significant correlation with the following J-IRLS subscales: discomfort in legs/arms, relief from moving around, sleep disturbance, severity as a whole, and average severity ($P = 0.0164$, 0.0033, 0.0314, 0.0273, and 0.0033, respectively). In addition, PSQI-J habitual sleep efficacy showed a weak but significant correlation with the following J-IRLS item scores: sleep disturbance, severity as a whole, and average severity ($P = 0.0210$, 0.0220, and 0.0046, respectively). J-IRLS impact on daily affairs showed a weak but significant correlation with PSQI-J daytime dysfunction ($P = 0.0351$). However, no significant correlation was observed between sleep latency and sleep disturbance on PSQI and any IRLS item scores.

Further exploration of multiple factor solutions on items of PSQI-J together with J-IRLS was performed on 56 patients at baseline. The first factor and second factor had an eigenvalue >1.0 (5.33, 1.67). The eigenvalue of the third factor was 0.87. The scree plot showed a clear break at the fourth factor. Therefore, we accepted three soluble factors, which accounted for 88.1% of the variance. Factor loading with oblique promax rotation and communality is shown in Table 4. Subscales were constructed from 10 items with both factor loadings of >0.4 and >0.15 of difference in the loading values from other factors. As a result, 10 items of J-IRLS were divided into two factors as follows: items 1, 2, 4, 6, and 8 appeared as the first factor and items 5 and 9 as the second factor. Among PSQI-J variables, item 1 (sleep quality) appeared as the first factor. Item 7 (daytime dysfunction) appeared as the second factor. Item 3 (sleep duration) and item 4 (habitual sleep efficiency) could not be categorized in the above two factors, and appeared as the third factor.

Responsiveness

The J-IRLS total score after 6 weeks of treatment was 11.7 ± 9.3, the change of J-IRLS total score from baseline to week 6 in 37 patients evaluated was 11.9 ± 9.6 and the correlation coefficients with CGI-I and PGI were 0.686 and 0.715, respectively (both $P <$ 0.0001). Changes in J-IRLS total score by CGI-I and PGI subgroups also showed significant differences (Fig. 1; $P = 0.0005$ and 0.0004, respectively; Kruskal–Wallis test). The effect sizes for 'very much improved' and 'much improved' on CGI-I were −3.2 and −1.7, respectively; those for 'very much better' and 'much better' on PGI were −3.1 and −1.8, respectively.

DISCUSSION

The value of ICC for sum score of J-IRLS in the present study was similar to that of the first validation report on the original version of IRLS made by IRLSSG,[7] suggesting that test–retest reliability of J-IRLS is stable over a certain time period.

Although the above report confirmed the test–retest reliability of the sum score of IRLS,[7] this is the first report to estimate the test–retest reliability of the

Table 4. Factor loadings of PSQI-J items and J-IRLS items

			Factor1	Factor2	Factor3	Communality
PSQI-J	1	Sleep quality	***0.485***	0.062	0.313	0.494
	2	Sleep latency	***0.327***	−0.222	0.121	0.139
	3	Sleep duration	0.141	−0.005	***0.655***	0.525
	4	Habitual sleep efficiency	0.134	−0.302	***0.777***	0.718
	5	Sleep disturbance	−0.148	0.100	***0.321***	0.09
	6	Daytime dysfunction	−0.044	***0.585***	−0.224	0.353
J-IRLS	1	Discomfort in legs/arms	***0.970***	−0.031	−0.12	0.836
	2	Need to move	***0.976***	−0.167	−0.25	0.714
	3	Relief from moving around	***0.304***	0.140	0.287	0.311
	4	Sleep disturbance	***0.471***	0.199	0.166	0.438
	5	Tiredness/sleepiness	0.104	***0.702***	0.037	0.574
	6	Severity as a whole	***0.772***	0.123	0.052	0.727
	7	How often	***0.312***	0.260	0.155	0.305
	8	Average severity	***0.513***	0.167	0.270	0.559
	9	Impact on daily affairs	−0.048	***0.771***	0.082	0.584
	10	Mood disturbance	0.419	***0.441***	−0.035	0.507

Factor loading was calculated by principal factor analysis with oblique promax rotation.
Factor loadings for the critical items are indicated in bold and italics.
J-IRLS, the Japanese version of International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome; PSQI-J, the Japanese version of the Pittsburgh Sleep Quality Index.

10 items of J-IRLS. Herein, all Kappa statistics for 10 items showed >0.4 of the values, suggesting that reliability of the J-IRLS 10 items is moderate or good.[14] Among lower items constructing the J-IRLS, 'need to move', 'relief from moving around', 'sleep disturbance', and 'mood disturbance' had moderate inter-rater reliability (weighted Kappa, 0.493–0.590).

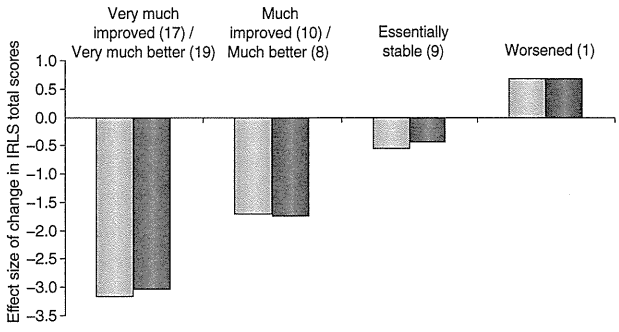

Figure 1. Responsiveness as determined by change in International Restless Legs Syndrome Study Group Rating Scale (IRLS) total score from baseline to week 6: effect sizes are compared among (□) Clinical Global Impression-Improvement (CGI-I) and (■) Patient Global Impressions (PGI) categories. 'Essentially stable' included 'Minimally improved', 'No change' and 'Minimally worse' on CGI-I, and 'A little better', 'No change' and 'A little worse' on PGI. 'Worsened' included 'Much worse' and 'Very much worse' on both CGI-I and PGI. $P = 0.0005$ for comparison among group for CGI and $P = 0.0004$ for those among PGI (Kruskal–Wallis test).

When evaluating internal consistency of J-IRLS, Cronbach's alpha was >0.90, consistent with the above-mentioned first validation report on IRLS.[7] Therefore J-IRLS is regarded as having good internal consistency.

Regarding the concurrent validity of the sum score of J-IRLS examined by comparing its value with CGI-S, the correlation coefficient in this study was consistent with that of the previous validation report.[7]

In this study, we found the two-factor structure for the J-IRLS 10 items, as reported previously.[8,15] The factors relevant to RLS symptoms mainly occurring at night and relevant to the impact of RLS symptoms on daily life were statistically distinguished. The reason for the discrepancies of results for item 3, 'RLS relief from moving around', among our findings and those of Allen *et al.*[15] and Abetz *et al.*[8] remains unclear. However, considering that tiredness and sleepiness (item 5) as well as mood disturbance (item 10) of RLS have been speculated to emerge as a daytime consequence of chronic sleep deprivation caused by the disorder,[16,17] it seems reasonable that these items belong to the symptom impact domain. The values of

ICC for these factors were also similar to the total score and were stable.

This study revealed that both J-IRLS and PSQI-J included some uncorrelated items, and that the total scores of J-IRLS and PSQI-J showed significant but small correlation. This phenomenon could be ascribed to the difference in the target domain between these two parameters. When evaluating factor structure of the items of PSQI-J together with those of J-IRLS, we found three distinct factor structures. Ten items of J-IRLS were included in the above-indicated RLS symptom domain and symptom impact domain. Cole *et al.*[18] previously reported that items of PSQI could be divided into three divisions. In this study, item 1 of PSQI-J (sleep quality) was classified as a symptom-related factor, item 7 (daytime dysfunction) as a symptom impact factor, and items 3 (sleep duration) and 4 (habitual sleep efficiency) appeared as a third factor indicative of sleep efficiency – as consistent with Cole's report.[18] This finding implies that additional use of PSQI-J among RLS patients may elicit further information regarding sleep disturbance that cannot be detected by J-IRLS alone.

The change of J-IRLS total score after treatment correlated well with both CGI-I and PGI, which is consistent with a previous report.[8] The effect sizes of the change of J-IRLS for CGI-I subgroups were also consistent with those reported by Abetz *et al.*[8] These findings strongly indicate that J-IRLS is a useful tool for evaluating symptom response to RLS-specific treatments.

Our study contained a number of limitations. First, this study was performed as a sub-study of a randomized, double-blind, placebo-controlled clinical trial of pramipexole, potentially leading to selection bias. Second, because the study sample comprised a considerable number of patients having low CGI-S, this phenomenon could lead to the increased weighted Kappa value. Nonetheless, J-IRLS demonstrated appropriate reliability and validity to evaluate RLS symptoms compatible with the original version of the scale. Moreover, J-IRLS was shown to have sufficient responsiveness to RLS treatment. Analysis of construct validity revealed that J-IRLS and PSQI-J share common domains for RLS-related symptoms and their impact on daily life; however, only PSQI-J was revealed to be powered to measure sleep efficiency. From these findings, we speculate that J-IRLS is valid for quantifying the severity of RLS in Japanese patients.

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Original Article

Efficacy and safety of rotigotine in Japanese patients with restless legs syndrome: a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group study

Yuichi Inoue [a,*], Tetsuo Shimizu [b], Koichi Hirata [c], Naohisa Uchimura [d], Jun Ishigooka [e], Yasunori Oka [f], Junji Ikeda [g], Takayuki Tomida [g], Nobutaka Hattori [h], for the Rotigotine Trial Group

[a] Department of Somnology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan
[b] Department of Neuropsychiatry, Akita University, 1-1 Tegata, Gakuen-machi, Akita 010-8502, Japan
[c] Department of Neurology, Dokkyo Medical University, 880 Kitakobayashi, Shimotsuga-gun, Mibumachi, Tochigi 321-0207, Japan
[d] Department of Neuropsychiatry, Kurume University, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
[e] Department of Psychiatry, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
[f] Department of Sleep Medicine, Ehime University Graduate School of Medicine, Tohon, Japan
[g] Otsuka Pharmaceutical Co., Ltd., 2-9 Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan
[h] Department of Neurology, Juntendo University Hospital, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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ABSTRACT

Objective: We aimed to ascertain the efficacy and safety of transdermal rotigotine (2 and 3 mg/24 h) in Japanese patients with restless legs syndrome (RLS).
Methods: In our double-blind placebo-controlled study, 284 Japanese patients with idiopathic RLS were randomly assigned to receive rotigotine 2 mg/24 h or 3 mg/24 h, or placebo, for 13 weeks. The primary endpoint was the change in International Restless Legs Syndrome Study Group rating scale (IRLS) total score.
Results: The placebo-subtracted decreases in IRLS total score for rotigotine 2 mg/24 h and 3 mg/24 h were −2.8 ± 1.3 and −3.1 ± 1.3, respectively, which were significant ($P < 0.05$). The interaction between baseline Pittsburgh Sleep Quality Index (PSQI) and treatment group for the change in IRLS total score was significant, indicating greater improvements in IRLS total score in patients with severe insomnia. Overall, 80.0%, 86.2%, and 51.6% of patients in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively, experienced adverse events (AEs) including application site reactions in 42.1%, 50.0%, and 7.4% of patients, respectively. None of the AEs were severe.
Conclusions: Our results showed that rotigotine was effective without major safety concerns at doses of up to 3 mg/24 h in Japanese patients with RLS.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder associated with abnormal sensations, particularly in the legs [1,2]. Patients often have a strong desire to move the affected extremities and these sensations are either completely or partially relieved by voluntary movements such as walking. These symptoms are aggravated at rest during the night and often lead to insomnia [3]. Serious RLS can result in daytime sleepiness or malaise associated with nocturnal sleep deprivation, resulting in deteriorated quality of life, depression, and anxiety disorders [4–6]. RLS is also known to be a risk factor for the development of cardiovascular disease [7,8]. Several epidemiologic surveys have been conducted using the International Restless Legs Syndrome Study Group (IRLSSG) and the National Institutes of Health (NIH) criteria [9] and revealed that the morbidity of RLS ranges from 5% to 10% in Western countries [4,10,11] and from 2% to 4% in Japan [12,13].

The four essential criteria for RLS established by the IRLSSG/NIH [9] are as follows: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) an urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) an urge to move or unpleasant sensations are partially or totally relieved by movements, such as walking or stretching, at least as long as the activity continues; and (4) an urge to move or

* Corresponding author. Tel.: +81 3 3351 6141.
E-mail address: inoue@somnology.com (Y. Inoue).

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unpleasant sensations that become clearly worse in the evening or at night than during the day or only occur during these periods.

For pharmacotherapy, dopamine receptor agonists are regarded as the first-line treatment of moderate to severe RLS [14–17]. Rotigotine is a non-ergot-derived dopamine agonist for all dopamine receptors (D1–D5), with highest affinity for the D3 dopamine receptor [18,19]. When formulated as a patch, stable plasma concentrations of the drug can be maintained over a 24-h period by continuous delivery [20], allowing control of RLS symptoms during both the daytime and the nighttime [21,22]. To date several clinical trials have been conducted in the United States and Europe to confirm the superiority of the treatment response with rotigotine to that with placebo [21,22]. However, such studies have not yet been conducted in Asian patients. Moreover, the effects of rotigotine on subjective insomnia associated with RLS have not been confirmed. For these reasons, we investigated the efficacy of rotigotine (2 mg/24 h and 3 mg/24 h) on RLS symptoms, the RLS-associated subjective sleep disturbances using an authorized sleep disturbance questionnaire, and the safety of rotigotine (2 mg/24h and 3 mg/24 h) in Japanese patients with idiopathic RLS.

2. Methods

2.1. Patients

Our phase 3, multicenter (44 institutions in Japan), randomized, double-blind, placebo-controlled, parallel-group study of Japanese patients with idiopathic RLS was conducted between February 2010 and December 2010. Patients who fulfilled the following inclusion criteria were enrolled: (1) ages 20 to <80 years at the time of providing informed consent, (2) diagnosis of RLS fulfilling all four items of the IRLSSG/NIH criteria, (3) responsive to prior dopaminergic therapy or no prior treatment for RLS, (4) baseline International Restless Legs Syndrome Study Group rating scale (IRLS) total score $\geqslant$15, and (5) RLS symptoms on $\geqslant$2 days per week for two consecutive weeks before entering the study.

Patients with any of the following criteria were excluded: (1) coexisting sleep disorders other than RLS; (2) somatic conditions that can cause secondary RLS, such as end-stage renal disease or iron deficiency (based on reference values; serum ferritin <18.6 ng/mL [reference range, 18.6–261 ng/mL] in males or <4.0 ng/mL [reference range, 4.0–64.2 ng/mL] in females); (3) concurrent neurologic disease (e.g., polyneuropathy, Parkinson disease, dementia); (4) psychiatric symptoms (e.g., hallucinations, delusions); and (5) symptoms of orthostatic hypertension. The concomitant use of drugs that could possibly affect RLS symptoms, including antiparkinsonian agents, psychoneurotropic agents, hypnotic sedatives, anxiolytic agents, antiepileptic drugs, opioid drugs, gastrointestinal agents with antagonistic effects on dopamine receptors, iron preparations, antihistamines, other central nervous system agents, drugs with opioid-like effects, clonidine, triptans for the treatment of migraine, and magnesium preparations, was prohibited [21,22]. Drugs that could cause QT prolongation (e.g., quinidine, procainamide, amiodarone, sotalol) were also prohibited. Patients were withdrawn from the study if they used any prohibited drugs for any length of time from 14 days before the start of study drug administration to the end of the treatment period. The use of less sedating antihistamines (fexofenadine and loratadine), vitamin B12, and folic acid was permitted during the study, but their dosing regimen was required to remain unchanged from 14 days before starting treatment to the end of the study period.

All patients were provided with an explanation of the study, including its purpose, procedures, and possible risk for adverse reactions or discontinuation, and they gave written informed consent to take part in the study before enrollment. Our study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was reviewed and approved by an institutional review board at each study site. The study was registered with Clinicaltrials.gov (identifier: NCT01084551) and the Japan Pharmaceutical Information Center (identifier, Japic CTI-101053).

2.2. Treatments

The patients were randomly assigned (1:1:1) to receive rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, or placebo. The doses of 2 and 3 mg/24 h were chosen for our study, as a previous dose-finding study in Japan found no significant difference in the efficacy between 1 mg/24 h and placebo (unpublished data; clinicaltrials.gov trial identifier NCT00666965). The study treatment period consisted of a 5-week dose titration period and an 8-week dose-maintenance period, followed by a dose-tapering period at a daily dose of 1 mg/24 h for up to 1 week. We used a fixed-dose titration method [21], in which the rotigotine dose was started at 1 mg/24 h and increased to 2 mg/24 h after 1 week; then the dose was increased to 3 mg/24 h after 2 weeks. After reaching the assigned dose in each group, sham titration was performed. After reaching a dose of 2 mg/24 h or higher, down titration to the previous dose level was permitted only once during the titration period if an intolerable adverse event (AE) occurred.

2.3. Endpoints

The primary endpoint was the change in the IRLS total score (Japanese Version 2.2) [23,24] from baseline to the end of treatment (EOT) at week 13. The proportion of IRLS responders was defined as patients with a $\geqslant$50% improvement in IRLS total score at the EOT compared with the score at baseline as a secondary end point [22]. Other secondary endpoints included improvements in Clinician Global Impression Improvement (CGI-I) and Patient Global Impression Improvement (PGI-I) scores [25], and the total score on the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) manifested the severity of subjective sleep disturbance, mainly insomnia [26,27]. Patients with a CGI-I or PGI-I rating of very much improved or much improved were defined as responders. A PSQI total score $\geqslant$5.5 was defined as pathologic sleep disturbance.

Safety assessments included AEs, and changes in laboratory tests, vital signs, 12-leads electrocardiography, skin irritation assessment [28], the Japanese version of the Epworth Sleepiness Scale completed by the patients to assess safety of sleepiness [29,30], physical and neurologic examinations, and the Japanese version of the modified Minnesota Impulsive Disorders Interview [31] to assess obsessive–compulsive disorders or impulse control disorders. Skin irritation was assessed based on the following six criteria [28]: (1) no reaction; (2) mild erythema; (3) erythema; (4) erythema and edema; (5) erythema plus edema plus papules, seropapules, or small vesicles; and (6) large vesicles.

2.4. Statistical analysis

Based on the results of a previous dose-finding trial of rotigotine in Japanese patients with RLS (unpublished data; clinicaltrials.gov trial identifier NCT00666965), the difference between the rotigotine and placebo groups in the change in IRLS total score from baseline to the EOT was assumed to be 4.5 with a standard deviation (SD) of 9.0 for the change in each group. Under these assumptions, we estimated that we would need a sample size of 80 patients per group to provide an overall power of at least 80% with

the closed testing procedure. Efficacy analyses were conducted on the full analysis set (FAS), which was defined as all patients who received at least one dose of study drug and underwent efficacy assessments at least once after starting treatment. The safety analysis set (SAS) consisted of all patients who received the study drug at least once. For efficacy analysis, the last observation carried forward approach was applied with the last observed value being entered as the missing value. For the primary endpoint, the closed testing procedure was used to maintain the overall significance level at 5% (two-tailed). Superiority was accepted if the upper limit of the 95% confidence interval [CI] was <0. Superiority of rotigotine 3 mg/24 h to placebo and that of rotigotine 2 mg/24 h to placebo were verified by *t*-tests. For the proportion of patients with a reduction of ⩾50% in IRLS total score from baseline, the difference between each rotigotine group and the placebo group was calculated using χ^2 tests. For secondary endpoints, the improvements in CGI-I and PGI-I were evaluated by calculating the numbers and proportions of patients defined as responders (very much improved or much improved). The improvement in PSQI total score was also evaluated by calculating the mean ± SD score and the proportion of patients with a score of <5.5 at the EOT. For secondary endpoints, the groups were compared using the Kruskal–Wallis test for continuous variables or χ^2 tests for categorical variables to provide further insight into the effects of rotigotine. Two-sided 95% CIs for the difference of groups were also calculated.

Possible interactions between the changes in IRLS total score or PSQI total score within each treatment group and baseline variables (sex, age, disease duration, baseline IRLS total score, and baseline PSQI total score) were evaluated using analysis of variance. The median IRLS total score at baseline (<23 vs ⩾23) or the median PSQI total score (<8 vs ⩾8) at baseline was used in our analysis. Subgroup analyses were conducted using factors that interacted with the treatment group.

Baseline characteristics were presented descriptively as mean ± SD or as frequencies. Safety endpoints were summarized using descriptive statistics. AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (Japanese Version 13.1).

3. Results

3.1. Patient characteristics

Of the 480 enrolled patients, 196 were withdrawn before randomization. Therefore, 284 were randomized with 95, 94, and 95 patients assigned to the rotigotine 2 mg/24 h, 3 mg/24 h, and the placebo groups, respectively (Fig. 1). All of these patients were included in the FAS and SAS. Down-titration was performed in five patients (5%) in the rotigotine 2 mg/24 h group and 10 patients (11%) in the 3 mg/24 h group. Treatment was discontinued in 31 patients (14, 8, and 9 patients in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively). The most common reason for discontinuation was AEs. Six patients ($n = 4$, rotigotine 2 mg/24 h; $n = 2$, placebo group) were withdrawn from the study because they used prohibited drugs during the treatment period. A total of 81 (85%), 86 (91%), and 86 (91%) patients completed the study in the rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, and placebo groups, respectively (Fig. 1).

The characteristics of the patients included in the FAS are shown in Table 1. The general characteristics of all three groups were similar except for age, as there tended to be more patients aged ⩾65 years in the placebo group than in both rotigotine groups. Most patients had de novo RLS, and <15% of patients in any group previously received any treatment for RLS, including dopamine receptor agonists, L-DOPA (Levodopa), or benzodiazepines (Table 1).

3.2. Efficacy

3.2.1. Primary endpoint

Fig. 2 shows the time course of changes in IRLS total score from baseline to the EOT. There were decreases in IRLS total scores in both rotigotine groups as early as week 1 in the titration phase, and the scores continued to decline until the EOT. The mean ± SD changes in IRLS total score from baseline to the EOT were −14.3 ± 8.9, −14.6 ± 9.0, and −11.6 ± 8.2 in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively.

The mean differences in the change in IRLS total score from baseline to the EOT between the rotigotine 2 mg/24 h group and

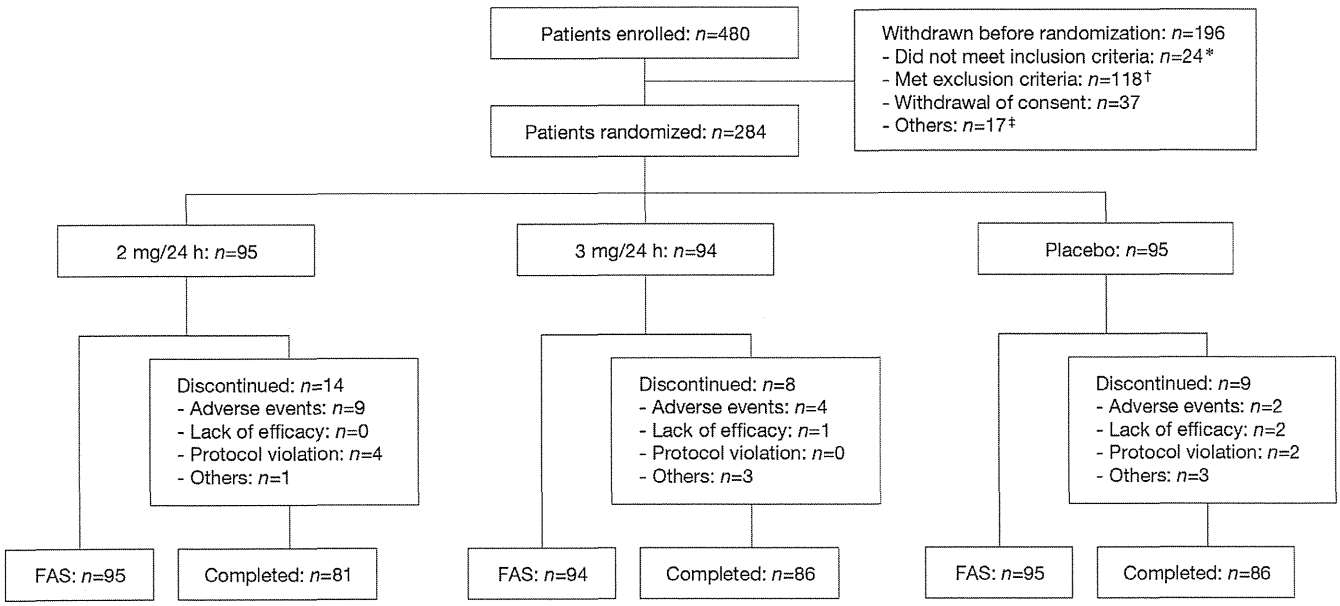

Fig. 1. Patient disposition. *Abbreviation:* FAS, full analysis set. *Mild/infrequent ($n = 22$) or doubtful ($n = 2$) RLS symptoms. †Includes iron deficiency ($n = 87$), echocardiogram parameters beyond the recommended range ($n = 11$), coexisting sleep disorders ($n = 7$), concurrent disease that can affect RLS symptoms ($n = 5$), or another exclusion criterion ($n = 5$). ‡Includes harmful events before starting drug administration ($n = 17$), the investigator's discretion ($n = 8$), or loss to follow-up ($n = 2$).

Table 1
Baseline characteristics of the patients in each treatment group (full analysis set).

	Rotigotine 2 mg/24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)	P value
Sex				
Male	41 (43.2)	48 (51.1)	41 (43.2)	0.453[a]
Female	54 (56.8)	46 (48.9)	54 (56.8)	
Age, years	50.7 ± 13.3	50.9 ± 13.7	53.4 ± 15.3	0.254[b]
<65 years	77 (81.1)	77 (81.9)	65 (68.4)	0.047[a]
⩾65 years	18 (18.9)	17 (18.1)	30 (31.6)	
Duration of disease morbidity, years	13.4 ± 13.1	12.5 ± 12.3	15.7 ± 14.4	0.185[b]
Time since diagnosis, years	0.6 ± 1.1	0.6 ± 1.2	0.7 ± 1.7	0.978[b]
IRLS total score	23.4 ± 5.3	22.7 ± 5.1	23.1 ± 4.9	0.664[b]
Moderate RLS (11–20)	30 (31.6)	36 (38.3)	31 (32.6)	0.676[a]
Severe RLS (21–30)	57 (60.0)	54 (57.4)	56 (58.9)	
Very severe RLS (31–40)	8 (8.4)	4 (4.3)	8 (8.4)	
PSQI total score	7.6 ± 3.0	7.6 ± 3.3	7.9 ± 3.0	
<5.5	23 (24.2)	22 (23.4)	21 (22.1)	0.942[a]
⩾5.5	72 (75.8)	72 (76.6)	74 (77.9)	
De novo RLS[c]	82 (86.3)	80 (85.1)	87 (91.6)	0.921[a]
Prior treatment for RLS	13 (13.7)	14 (14.9)	8 (8.4)	0.354[a]
Dopamine receptor agonists	7 (7.4)	11 (11.7)	7 (7.4)	0.479[a]
L-dopa	1 (1.1)	0	0	0.369[a]
Benzodiazepines	4 (4.2)	3 (3.2)	1 (1.1)	0.406[a]
Other drugs	4 (4.2)	2 (2.1)	1 (1.1)	0.361[a]

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; RLS, restless legs syndrome; PSQI, Pittsburgh Sleep Quality Index; L-dopa, Levodopa. Values are expressed as mean ± standard deviation for continuous variables or n (%) for categorical variables.
[a] χ^2 test.
[b] Kruskal–Wallis test.
[c] Patients not previously treated for RLS.

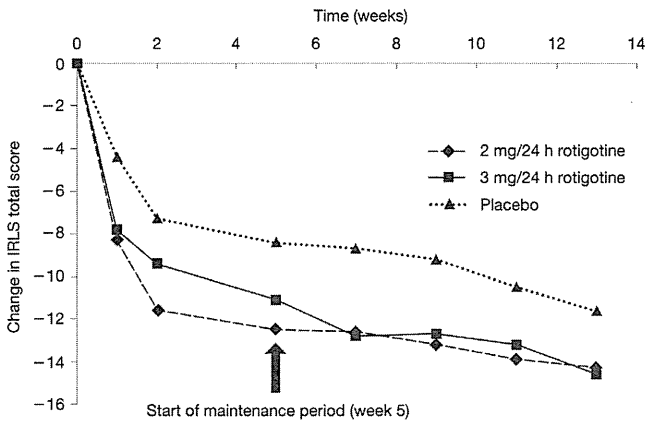

Fig. 2. Changes in IRLS rating scale total scores during the dose maintenance period (full analysis set, last observation carried forward). The analysis of the primary endpoint was performed using the scores recorded at week 13.

the placebo group and between the rotigotine 3 mg/24 h group and the placebo group were −2.8 ± 1.3 (95% CI, −5.3 to −0.3) and −3.1 ± 1.3 (95% CI, −5.6 to −0.6), respectively (Table 2). The upper limit of the 95% CI was below 0, demonstrating the superiority of both rotigotine doses to placebo. The proportions of IRLS responders were 60.2%, 66.0%, and 47.4% in the rotigotine 2 mg/24 h, rotigotine 3 mg/24 h, and placebo groups, respectively.

3.2.2. Secondary endpoints

The mean changes in PSQI total score from baseline to the EOT in the rotigotine 2 mg/24 h and 3 mg/24 h groups were −3.1 ± 3.2 and −3.2 ± 3.3, respectively, which were not significantly different from the change in the placebo group (−2.5 ± 2.4). However, the proportions of patients with a PSQI total score of <5.5 at the EOT were 77.4% (72/93 patients), 74.4% (67/90 patients), and 56.4% (53/94 patients) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The proportions of patients with a PSQI total score of <5.5 at the EOT were significantly greater in both rotigotine groups than in the placebo group (Table 2). The proportions of patients with CGI-I or PGI-I rated as much improved or very much improved (CGI-responders and PGI-I responders, respectively) in the rotigotine 2 mg/24 h group were not significantly different from those in the placebo group. On the other hand, the proportions of CGI-I and PGI-I responders were significantly greater in the rotigotine 3 mg/24 h group than in the placebo group.

3.2.3. Factors interacting with the primary endpoint

In interaction analyses, the interaction between the baseline IRLS total score and treatment group was not statistically significant for the change in IRLS total score (Table 3). However, the interaction between the baseline PSQI total score and treatment group was statistically significant for the change in IRLS total score (P < 0.01). The changes in IRLS total scores in patients with less severe insomnia (i.e., baseline PSQI total score <8) were −12.9 (95% CI, −15.1 to −10.7), −11.7 (95% CI, −13.9 to −9.5), and −12.3 (95% CI, −14.7 to −9.9) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. In patients with more severe insomnia (i.e., baseline PSQI total score ⩾8), the changes were −16.0 (95% CI, −18.8 to −13.3), −18.3 (95% CI, −21.1 to −15.6), and −11.0 (95% CI, −13.4 to −8.5) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The changes in IRLS total scores in both rotigotine groups were greater than those in the placebo group in patients with more severe insomnia.

The interaction between the baseline PSQI total score and treatment group was also statistically significant for the change in PSQI total score (P < 0.01). The changes in PSQI total scores in patients with less severe insomnia were −1.5 (95% CI, −2.1 to −0.9), −1.4 (95% CI, −1.9 to −0.8), and −1.8 (95% CI, −2.4 to −1.2) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. In patients with more severe insomnia, the changes were −5.0 (95% CI, −5.9 to −4.1), −5.4 (95% CI, −6.3 to −4.5), and −3.2 (95% CI, −4.0 to −2.3) in the rotigotine 2 mg/24 h, 3 mg/24 h, and placebo groups, respectively. The changes in PSQI total scores in both rotigotine groups were also greater than those in the placebo group in patients with more severe insomnia.

3.3. Safety

Overall, 80.0% (76/95) of patients in the rotigotine 2 mg/24 h group, 86.2% (81/94) of patients in the rotigotine 3 mg/24 h group, and 51.6% (49/95) of patients in the placebo group experienced AEs (Table 4).

AEs occurring with an incidence of ⩾5% in any group are listed in Table 4. The most common AE was application site reaction, which was more frequent in both rotigotine groups compared with the placebo group. Other AEs, including nausea, vomiting, and somnolence, were also frequent in both rotigotine groups. Nine patients (9.5%) in the rotigotine 2 mg/24 h group, four patients (4.3%) in the rotigotine 3 mg/24 h group, and two patients (2.1%) in the placebo group discontinued treatment due to AEs. Application site reactions were the most common AEs responsible for treatment discontinuation and were responsible for discontinuation in four patients in the rotigotine 2 mg/24 h group and one patient in the rotigotine 3 mg/24 h group. Other events leading to discontinuation included nausea, gastritis, insomnia, sudden onset of sleep, and worsening of RLS symptoms in one patient each in the

Table 2
IRLS response rate and improvements in IRLS score according to the severity of RLS or sleep disturbances.

	Change from baseline (mean ± SD or%)[a]			Rotigotine vs placebo (LS mean or %)[b]			
	Rotigotine 2 mg/24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)	Rotigotine 2 mg/24 h		Rotigotine 3 mg/24 h	
				Difference (95% CI)	P value	Difference (95% CI)	P value
IRLS total score	−14.3 ± 8.9	−14.6 ± 9.0	−11.6 ± 8.2	−2.8 (−5.3 to −0.3)	0.030	−3.1 (−5.6 to −0.6)	0.016
PSQI total score	−3.1 ± 3.2	−3.2 ± 3.3	−2.5 ± 2.4	−0.6 (−1.4 to 0.3)	0.188	−0.7 (−1.6 to 0.2)	0.112
IRLS responders[c]	60.2	66.0	47.4	12.8 (−1.3 to 27.0)	0.077	18.6 (4.7 to 32.5)	0.010
PSQI total score <5.5 (%) at the EOT	77.4	74.4	56.4	21.0 (7.9 to 34.2)	0.002	18.1 (4.6 to 31.5)	0.010
CGI-I responders (%)[d]	67.7	74.2	57.9	9.8 (−3.9 to 23.6)	0.163	16.3 (3.0 to 29.6)	0.018
PGI-I responders (%)[d]	73.1	80.6	62.1	11.0 (−2.3 to 24.3)	0.107	18.5 (5.9 to 31.2)	0.005

Abbreviations: SD, standard deviation; LS, least squares; CI, confidence interval; IRLS, International Restless Legs Syndrome Study Group rating scale; PSQI, Pittsburgh Sleep Quality Index; EOT, end of treatment; CGI-I, Clinician Global Impression improvement; PGI-I, Patient Global Impression improvement.
[a] Values are expressed as mean ± standard deviation for continuous variables or % of patients for categorical variables.
[b] Values are least-squares means for continuous variables or % of patients for categorical variables.
[c] % of patients with a ⩾50% improvement in IRLS total score at the EOT compared with baseline.
[d] % of patients with CGI-I or PGI-I rated as very much improved or much improved.

Table 3
Interaction between treatment group and baseline variables for the improvements of IRLS total score or PSQI total score.

Interaction	Change in IRLS total score P value[a]	Change in PSQI total score P value[a]
Sex (male vs female) × treatment group	0.629	0.807
Age (<65 years vs ⩾65 years) × treatment group	0.664	0.596
Time since diagnosis (<1 year vs ⩾1 year) × treatment group	0.503	0.700
Baseline IRLS total score (as a continuous variable) × treatment group	0.090	0.228
Baseline IRLS total score (median, <23 vs ⩾23) × treatment group	0.117	0.429
Baseline PSQI total score (as a continuous variable) × treatment group	0.001	<0.001
Baseline PSQI total score (median, <8 vs ⩾8) × treatment group	0.006	0.001

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; PSQI, Pittsburgh Sleep Quality Index.
[a] Analysis of variance.

Table 4
Adverse events occurring with an incidence of ⩾5% in at least one group.

	Rotigotine 2 mg/c24 h (n = 95)	Rotigotine 3 mg/24 h (n = 94)	Placebo (n = 95)
Any adverse event	76 (80.0)	81 (86.2)	49 (51.6)
Application site reaction[a]	40 (42.1)	47 (50.0)	7 (7.4)
Nausea	32 (33.7)	41 (43.6)	9 (9.5)
Nasopharyngitis	12 (12.6)	16 (17.0)	12 (12.6)
Somnolence	10 (10.5)	14 (14.9)	2 (2.1)
Vomiting	4 (4.2)	10 (10.6)	1 (1.1)
Headache	5 (5.3)	2 (2.1)	0

Values are expressed in n (%).
[a] Corresponds to the Medical Dictionary for Regulatory Activities term, application and instillation site reactions.

rotigotine 2 mg/24 h group; somnolence, palpitation, increased blood creatine phosphokinase, and cold sweats in one patient each in the rotigotine 3 mg/24 h group; and lacunar infarction and agitation in one patient each in the placebo group.

Serious AEs included two events (road traffic accident and contusion due to accumulated nocturnal sleep loss) in one patient in the rotigotine 3 mg/24 h group and lacunar infarction and facial nerve paralysis, most likely due to viral infection, in one patient each in the placebo group. A possible relationship to the study drug was ruled out for all of these events, except the lacunar infarction in one patient in the placebo group. There were no deaths in our study.

For skin irritation, large vesicles were not observed in any group. One patient assigned to rotigotine 2 mg/24 h group exhibited erythema, edema, papules, seropapules, and small vesicles at week 5 of treatment. However, these signs had reverted to mild erythema at the following visit without requiring a reduction in rotigotine dose. Skin irritation did not exceed erythema in the majority of patients.

4. Discussion

Our study was conducted to confirm the superiority of rotigotine at doses of 2 mg/24 h and 3 mg/24 h to placebo; both doses were found to be superior to placebo in the improvement in IRLS total score from baseline to the EOT. Notably a larger proportion of patients experienced a ⩾50% improvement in IRLS total score in both rotigotine groups compared with the placebo group. The mean changes in IRLS total scores in our study were −14.3 and −14.6 for the rotigotine 2 mg/24 h and the 3 mg/24 h groups, respectively. These results are consistent with those reported in a similarly designed study conducted in European patients, in which the corresponding values were −16.2 and −16.8 [22]. Overall 60.2% and 66.0% of patients in the rotigotine 2 mg/24 h and the 3 mg/24 h groups, respectively, were defined as IRLS responders in our study, compared with 57.8% and 55.4% in the European study. The proportions of patients with a PSQI total score within normal range (i.e., PSQI <5.5) at the EOT were higher in both rotigotine groups compared with the placebo group, supporting the finding that the effectiveness of rotigotine yielded a certain improvement of insomnia at the EOT. However, it must be noted that the placebo group in our study showed a relatively large effect, as reported elsewhere [32]. In our study, the mean change in IRLS total score and the proportion of IRLS responders were −11.6% and 47.4%, respectively, in the placebo group, both of which were larger than the values of −8.6% and 25.4% in the European study [22]. One possible explanation for this finding is that we included a larger proportion of patients with de novo RLS [32], unlike the earlier studies.

The PSQI is a scale used to evaluate insomnia symptoms and shows high sensitivity [26,27]. In our study, we evaluated insomnia symptoms using the PSQI; however, other scales including the RLS-6 (single item) and Medical Outcomes Study Sleep Scale were used in previous rotigotine studies [21,22]. Using this scale, we conducted interaction analyses to identify the factors that could influence the changes in IRLS and PSQI total scores. In these analyses, the baseline PSQI total score and treatment group were significantly associated with the improvements in PSQI and IRLS total scores. In other words, the improvements in IRLS among patients with more severe insomnia (i.e., PSQI $\geqslant$8) were greater in both rotigotine groups than in the placebo group. Patients with more severe insomnia also showed a greater improvement in insomnia symptoms following treatment with rotigotine. These findings indicate that the PSQI scale may be relatively important for predicting the outcomes of rotigotine treatment for RLS.

In our study, AEs were observed in 80.0% of patients in the rotigotine 2 mg/24 h group, 86.2% of patients in the rotigotine 3 mg/24 h group, and 51.6% of patients in the placebo group. The incidence rates of nausea, vomiting, somnolence, and application site reaction were higher than the placebo group in both of the rotigotine groups, and the rates seemed to be higher in the 3 mg/24 h group than in the 2 mg/24 h group. Nausea, vomiting, and somnolence are known to be associated with the pharmacological action of dopaminergic drugs. Meanwhile application site reactions are specific to the patch formulation. In our study, application site reactions occurred in 42.1% and 50.0% of patients in the rotigotine 2 mg/24 h and 3 mg/24 h groups, respectively, and these rates are similar to those obtained in the European study [22]. Overall, the AE profiles of rotigotine in our study generally were comparable with those reported in other studies of rotigotine in the United States and Europe [21,22]. Thus rotigotine generally appears to be well-tolerated in Japanese patients with RLS.

There is one limitation of our study that warrants mention, namely, the assessment of sleep disturbances using the PSQI. In our study, the patients were asked to subjectively evaluate their sleep disturbances over the preceding 2 weeks, even though evaluation over a 1-month period was originally proposed by Buysse et al. [26].

Our study confirmed that rotigotine at 2 mg/24 h and 3 mg/24 h was superior to placebo in improving IRLS total score in Japanese patients with RLS. The reduction of RLS disease severity was associated with concomitant improvements in sleep disturbances. Both doses of rotigotine generally were well-tolerated and no serious AEs were observed with either dose.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.07.007.

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PLOS ONE

Differences in Brain Morphological Findings between Narcolepsy with and without Cataplexy

Masaki Nakamura[1,2]*, Shingo Nishida[1,2], Kenichi Hayashida[1], Yoichiro Ueki[1], Yves Dauvilliers[3], Yuichi Inoue[1,2]

1 Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan, **2** Tokyo Medical University, Department of Somnology, Tokyo, Japan, **3** National Reference Network for Narcolepsy, Sleep-Disorders Center, Department of Neurology, Hôpital Gui de Chauliac, Inserm U1061, UM1, Montpellier, France

Abstract

Objective: Maps of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) obtained by diffusion tensor imaging (DTI) can detect microscopic axonal changes by estimating the diffusivity of water molecules using magnetic resonance imaging (MRI). We applied an MRI voxel-based statistical approach to FA and ADC maps to evaluate microstructural abnormalities in the brain in narcolepsy and to investigate differences between patients having narcolepsy with and without cataplexy.

Methods: Twelve patients with drug-naive narcolepsy with cataplexy (NA/CA), 12 with drug-naive narcolepsy without cataplexy (NA w/o CA) and 12 age-matched healthy normal controls (NC) were enrolled. FA and ADC maps for these 3 groups were statistically compared by using voxel-based one-way ANOVA. In addition, we investigated the correlation between FA and ADC values and clinical variables in the patient groups.

Results: Compared to the NC group, the NA/CA group showed higher ADC values in the left inferior frontal gyrus and left amygdala, and a lower ADC value in the left postcentral gyrus. The ADC value in the right inferior frontal gyrus and FA value in the right precuneus were higher for NA/CA group than for the NA w/o CA group. However, no significant differences were observed in FA and ADC values between the NA w/o CA and NC groups in any of the areas investigated. In addition, no correlation was found between the clinical variables and ADC and FA values of any brain areas in these patient groups.

Conclusions: Several microstructural changes were noted in the inferior frontal gyrus and amygdala in the NA/CA but not in the NA w/o CA group. These findings suggest that these 2 narcolepsy conditions have different pathological mechanisms: narcolepsy without cataplexy form appears to be a potentially broader condition without any significant brain imaging differences from normal controls.

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* E-mail: nakamura@somnology.com

Introduction

Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement(REM) sleep manifestations [1]. Dysregulation of the hypocretinergic system plays an important role in the pathogenesis of human narcolepsy-cataplexy [2,3].

Some Previous neuroimaging studies have attempted to clarify the mechanisms of the brain dysfunction in narcolepsy. For example, in a study by Asenbaum et al., single photon emission computed tomography (SPECT) showed increased blood flow in the right hemisphere and decreased blood flow in the thalamus during REM sleep in patients with narcolepsy [4]. In another study that used positron emission tomography (PET), cerebral perfusion was found to be reduced in the bilateral anterior hypothalami, prefrontal cortices, cingulated gyri, and many other midbrain structures [5]. Furthermore, cerebral glucose Hypometabolism in the hypothalamic-thalamic-orbitofrontal pathways in narcolepsy was reported by Joo et al [6]. These studies have indicated that dysfunction of the midbrain and prefrontal cortices might be associated with narcolepsy pathology, however, the results were still conflicting.

With regard to brain morphological studies on narcolepsy-cataplexy, Desseilles et al. reported volumetric changes mainly in hypothalamic gray matter and/or the frontal cortex [7]. However, Overeem et al. reported no differences in hypothalamic volume between patients with hypocretin-deficient narcolepsy and controls [8]. Thus, brain morphometric changes in narcolepsy are still under debate.

In the second edition of the International Classification of Sleep Disorders (ICSD-2), narcolepsy was divided into 2 separate entities: i.e., narcolepsy with and without cataplexy. Narcolepsy without cataplexy differs from the former condition not only in terms of the absence of cataplexy but also in clinical (less severe

EDS), biological (low CSF-hypocretin-1 levels in 10–20% of cases) and neurophysiological (lesser increase of REM sleep propensity) characteristics [3,9–11]. A histopathological study indicated that hypocretin fiber density in the anterior hypothalamus was decreased in narcolepsy with cataplexy, but it was normal in narcolepsy without cataplexy [12]. This finding may suggest that the differences in clinical characteristics between narcolepsy with and without cataplexy are related to the difference in hypocretin fiber density in the anterior hypothalamus. However, all previous neuroimaging narcolepsy studies were conducted exclusively in patients with narcolepsy with cataplexy. To the best of our knowledge, brain morphological and microstructural differences have never been studied in patients having narcolepsy with and without cataplexy.

Diffusion tensor imaging (DTI) can identify the microstructural changes in neurons, as indicated by the values obtained for fractional anisotropy (FA) and apparent diffusion coefficient (ADC) [13]. FA values represent tract directionality and integrity of neuronal fibers, being sensitive to the number, coherence, and degree of myelination of neural fibers [13]. ADC values reflect microscopic water molecule diffusivity, and a high ADC value is thought to represent an increase in extracellular space and indicates microstructural changes in neurons [13]. In the current study, we applied a voxel-based statistical approach to FA and ADC maps of patients having narcolepsy with and without cataplexy to evaluate brain microstructural differences.

Methods

This study was approved by the ethics committees of the Neuropsychiatric Research Institute. All participant provided written informed consent before entering this study.

Twelve Japanese drug-naive patients having narcolepsy with cataplexy (NA/CA), 12 drug-naive patients having narcolepsy without cataplexy (NA w/o CA) and 12 non-obese healthy controls without EDS (NC) matched for age and sex were enrolled from April 2008 to December 2009 (Table 1). NA/CA and NA w/o CA were diagnosed according to the criteria outlined in the ICSD-2 [14]. To ensure accurate diagnoses, cataplexy symptoms were confirmed through detailed clinical interviews by 2 or more board-certified physicians who are specialized in sleep medicine. All patients underwent multiple sleep latency test (MSLT) following nocturnal polysomnography (PSG). Mean latencies of both sleep and REM sleep onset were analyzed in 4 or 5 nap trials on MSLT, according to a standard method [15]. All patients were asked to record their sleep time on sleep logs during a 2-week period before PSGs to ensure that they had no sleep insufficiency and that they all had slept for more than 6 hours on all the PSG nights. None of the patients had sleep apnea or periodic limb movements during sleep (apnea-hypopnea index<5/h, periodic limb movements index<15/h,) or any medical disorders that could cause narcolepsy-like sleepiness. All subjects had normal findings on physical and neurological examinations, and they had no comorbid psychiatric disorders, including depression and REM sleep behavior disorder.

MRI acquisition

MRI was performed using a 1.5T (GE Medical Systems) scanner with a conventional head coil. The T1-weighted images were obtained by a spin-echo sequence using the following parameters; repetition time (TR), 1,930 msec; echo time (TE), 13 msec: inversion time, 900 ms; flip angle 90°;, and matrix size, 512×512. DTI was performed by a fat suppressed spin-echo type single-shot echo-planer with a TR of 11,000 ms, a TE of 81 and slice thickness of 3.5 mm, without an interslice gap. Motion probing gradients (MPGs) for DTI were applied in 17 noncollinear directions ($b = 1000$ s/mm^2) after the acquisition of $b = 0$ s/mm^2 (b0) images. The transverse slices were aligned to the anterior-posterior commissure(AC-PC line) line. All subjects underwent brain MRI examinations during the daytime, in an awake condition, before receiving treatments.

FA and ADC maps preprocessing and statistics

The DTI data were transferred to an off-line windows PC with a Intel Core2 Extreme Quad CPU (2.27GHz) and 8.0 GB of memory for post-processing. FA and ADC maps were calculated using the dTV-II (Image Computing and Analysis Laboratory, Department of Radiology, University of Tokyo Hospital, http://www.ut-radiology.umin.jp/people/masutani/dTV.htm) [16] and VOLUME-ONE software. MRI T2-weighted template was used to spatially normalize these FA and ADC maps. The normalized FA and ADC maps were smoothed with FWHM (full-width-half-maximum) of 12 mm to increase the signal/noise ratio. These normalizing and soothing methods were implemented according to the spatial normalization and smoothing procedure included in SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) running in MATLAB 7.11 R2010b (The MathWorks; Natick, MA, USA).

Each normalized and smoothed FA and ADC maps were compared by using voxel-based between-subjects one-way ANOVA in SPM8 with global normalization by whole brain volume as a covariate among NA/CA, NA w/o CA and NC groups. An absolute threshold mask of 0.2 was used to avoid possible edge effects around the border between the gray and white matter. The significance level was set at $p < 0.001$ (uncorrected) for peak level on ANOVA. After conducting the ANOVA, in order to investigate significant main effects, multiple voxel-wise comparisons between NA/CA and NA w/o CA, between NA/CA and NC, and between NA w/o CA and NC were performed with post-hoc tests in cluster-level using family-wise error corrected p value ($P_{FWE\text{-}corr}$) <0.05 to protect against the occurrence of overall Type I Error. Gaussian random fields theory and Bonferroni procedure were also used to control the FWE rate by assuming that the data follow certain specified patterns of spatial variance and that the statistical distributions mimic a smoothly varying random field.

Correlation analyses were performed for the NA/CA group by using voxel-based multiple regression analysis in SPM8 with a significance level of $p < 0.05$ in cluster level between significant regions detected with FA/ADC maps. Correlation analyses were also performed with respect to age, gender, duration of narcolepsy, age at onset, frequency of cataplexy, sleepiness score as assessed by the Japanese version of the Epworth sleepiness scale(JESS) [17], and both sleep onset latency and the number of sleep onset REM periods (SOREMPs) on MSLT.

Results

Clinical and demographic data

Mean age and gender distribution were similar between the NA/CA, NA w/o CA and NC groups. Age at onset of EDS, duration of NA, mean JESS score, sleep onset REM (SOREM) latency and frequency of SOREMP period on MSLT (percentage of naps with SOREMP per total number of naps) did not differ between NA/CA and NA w/o CA groups (Table 1). Body mass index (BMI) was higher and sleep onset latency on MSLT was shorter in the NA/CA group than in the NA w/o CA group. Ten out of 12 patients having NA/CA reported to have sleep paralysis (83.3%), and all 12 patients had episodes of hypnagogic/

Table 1. Clinical and neurophysiological data of patients having narcolepsy with and without cataplexy.

	Narcolepsy with cataplexy	Narcolepsy without cataplexy	Normal Control
Sample size	12	12	12
Male: female	9:3	6:6	6:6
Age (years)	29.4±4.9	26.0±5.2	29.8±2.2
Age range (years)	(22–40)	(20–35)	(26–34)
Body mass index (BMI)	24.0±2.4*	21.3±1.8	
JESS score	18.5±3.1	17.9±5.1	
MSLT parameters			
Sleep onset latency (minutes)	1.1±0.6*	2.6±1.7	
Latency of Sleep onset REM (minutes)	3.7±3.4	5.7±3.4	
Frequency of SOREM period (%)	90.1±15.6	81.3±18.8	
Onset age of EDS (years)	18.2±7.4	16.0±3.4	
Duration of narcolepsy (years)	11.3±4.6	10.0±7.3	
Sleep paralysis	10/12	8/12	
Hypnagogic/hypnopompic hallucinations	12/12	8/12	
Apnea hypopnea index (per hour)	3.1±2.4	2.1±3.3	
Periodic legs movement index (per hour)	4.1±7.2	0.2±0.6	

Continuous values are expressed as mean±SD.
*p<0.05(t-test).
JESS: Epworth Sleepiness Scale, Japanese version.
MSLT: multiple sleep latency test.
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hypnopompic hallucinations. Among the 12 patients having NA w/o CA, sleep paralysis and hypnagogic/hypnopompic hallucinations were reported by 8 (66.7%) and 7 (58.4%) patients, respectively. All patients were drug-naive at the time of PSG and MRI examinations.

Comparison of brain images among narcolepsy with cataplexy, narcolepsy without cataplexy and normal controls

SPM-one-way ANOVA for the NA/CA, NA w/o CA and NC groups revealed significant differences in ADC values for the right inferior frontal gyrus [$F(2,32) = 17.76$, uncorrected $p<0.001$], left inferior frontal gyrus [$F(2,32) = 14.17$, uncorrected $p<0.001$], left parahippocampal gyrus and amygdala [$F(2,32) = 13.90$, uncorrected $p<0.001$], and left postcentral gyrus [$F(2,32) = 21.00$, uncorrected $p<0.001$]. The results of post-hoc tests with multiple voxel-wise comparisons indicated that the ADC value for the right inferior frontal gyrus was higher in the NA/CA than in the NA w/o CA group ($P_{FWE\text{-}corr} = 0.028$), and ADC values for the left inferior frontal gyrus, left parahippocampal gyrus and amygdala ($P_{FWE\text{-}corr} = 0.000$) were heigher in the NA/CA group compared to the NC group (Table 2, Figure 1, 2). In contrast, the ADC values for the left postcentral gyrus were lower in the NA/CA than in the NC group ($P_{FWE\text{-}corr} = 0.015$). FA values for the right parietal lobe (precuneus) significantly differed between the 2 NA groups [$F(2,32) = 13.87$, uncorrected $p<0.001$], with higher value in the NA/CA than in the NA w/o CA group on post-hoc test ($P_{FWE\text{-}corr} = 0.008$) (Table 2, Figure 2). No significant differences

Table 2. Significant differences in the ADC and FA values for the NA/CA, NA w/o CA, and NC groups.

			Brodmann area	Talairach coordinate	Cluster-level		
Contrast	**Image**	**Anatomical Region**		**x, y, z**	**F**	**$P_{FWE\text{-}corr}$**	**P_{uncorr}**
NACA>NC	ADC	Left inferior frontal gyrus	47,11	−20, 26, −18	14.17	0.000	0.000
		Left parahippocampal gyrus/ amygdala	34	−30, 4, −14	13.90	0.000	0.000
NACA<NC	ADC	Left postcentral gyrus	3	−20, −30, 72	21.00	0.015	0.002
NACA>NA w/o CA	ADC	Right inferior frontal gyrus	9	60, 8, 30	17.76	0.028	0.004
	FA	Right parietal lobe (precuneus)	7	8, −48,44	13.87	0.008	0.001

Height threshold uncorrected $p<0.001$ in peak level on ANOVA.
Group main effects in cluster-level by multiple voxel-wise comparisons using $P_{FWE\text{-}corr}$: family-wise error, corrected p.
NA/CA: narcolepsy with cataplexy, NA w/o CA: narcolepsy without cataplexy, NC: normal controls.
ADC: apparent diffusion coefficient, FA: fractional anisotropy.
doi:10.1371/journal.pone.0081059.t002

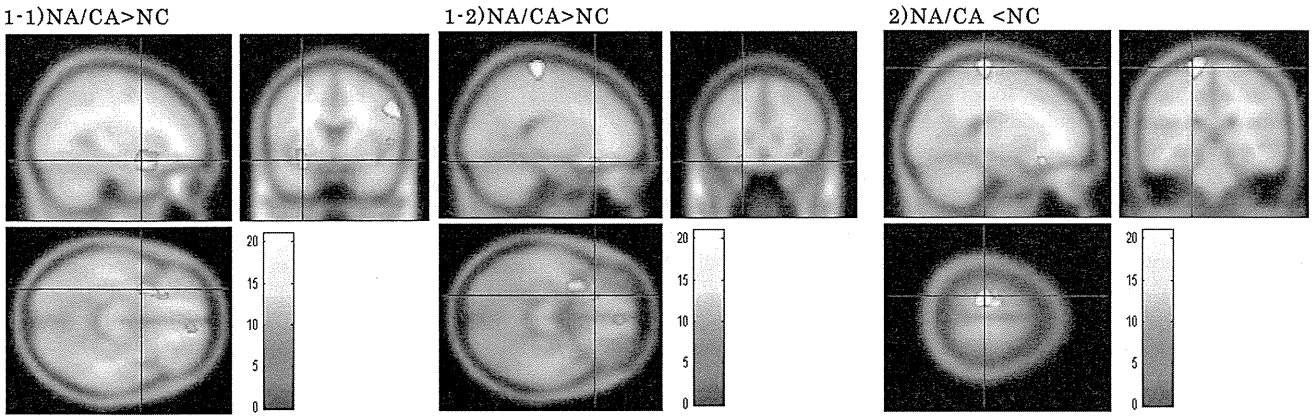

Figure 1. Clusters showing significant main effects of group on ADC value between patients having narcolepsy with cataplexy (NA/CA) and normal control (NC). 1-1) ADC values were higher in the left parahippocampal gyrus (Brodmann area 34) and amygdala, and 1-2) in the left inferior frontal gyrus (Brodmann area 47/11) in NA/CA than in NC, while these values were lower in 2) the left postcentral gyrus (Brodmann area 3) in the former group. pone.0081059.Results.tifare significant at FWE-corrected $p<0.05$. Color scale is for F statistic.
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were found in the ADC, or FA values for any brain areas between the NA w/o CA and NC groups.

Finally, no significant correlations were found between variables such as age, gender, duration of narcolepsy, age at onset, frequency of cataplexy, JESS score, sleep onset latency, and the number of SOREMPs on MSLT, and the ADC and FA values for any brain areas in the NA/CA group.

Discussion

Some previous voxel-based morphometry (VBM) studies indicated a volume reduction in the hypothalamus of patients with narcolepsy [7]. Significant neuronal loss in this area was also reported by MR spectroscopy in patients with narcolepsy-cataplexy [18]. In the present study, however, no microstructural changes were observed in the hypothalamus of patients with narcolepsy. Thannickal et al. reported an 85–95% reduction in the number of hypocretin neurons in the hypothalamus along with gliosis in patients with narcolepsy compared to normal population [19,20]. Considering that hypocretin neurons are distributed mainly in the hypothalamic area but do not form a nucleus [21], the degenerative loss of hypocretin neurons with gliosis in the hypothalamus of patients with narcolepsy is thought to be undetectable by millimeter-sized voxel-based MRI. This speculation has been supported by a study in which no significant structural changes were observed in the hypothalamus by using both VBM and small-volume correction analysis in patients with hypocretin-deficient narcolepsy [8]. Recently, a neuroimaging study used DTI indicated increased mean diffusivity (MD) without FA changes in the hypothalamus of the patients having narcolepsy with cataplexy, suggesting an increase in extracellular fluid space without further deformation [22]. In contrast, another DTI study showed a decreased FA value in the hypothalamus and brainstem in narcolepsy with cataplexy [23]. Meanwhile, our study did not

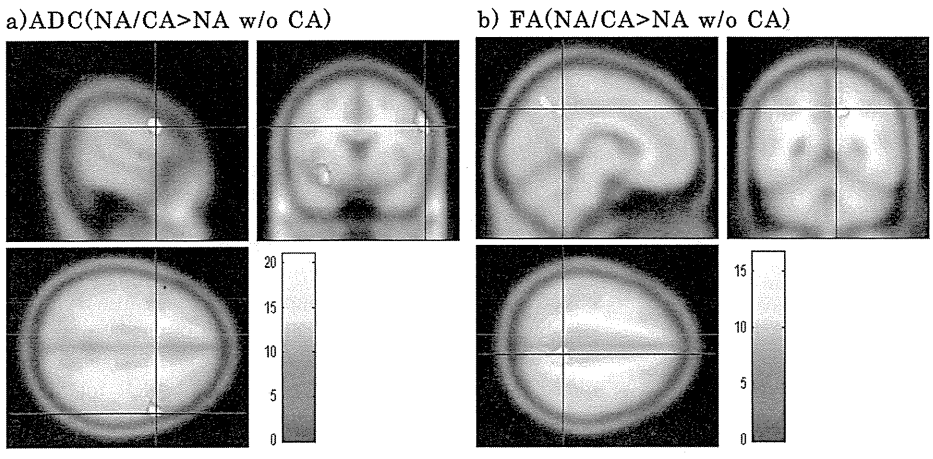

Figure 2. Clusters showing significant main effects of group on ADC and FA values between the narcolepsy with cataplexy (NA/CA) and narcolepsy without cataplexy (NA w/o CA) groups. a) ADC value was higher in the right inferior frontal gyrus (Brodmann area 9) for the NA/CA group than for the NA w/o CA group. b) In the NA/CA group, the FA value in the right parietal lobe (precuneus) was higher than that in the NA w/o CAgroup. Results are significant at FWE-corrected $p<0.05$. Color scale is for F statistic.
doi:10.1371/journal.pone.0081059.g002

show any abnormality in diffusion indices (ADC and FA) in the hypothalamus or brainstem. This discrepancy among the study results may be attributable to the differences in the method of calculating the diffusion index (MD or ADC), and/or to differences in the populations tested. In the previous 2 studies, the patients with narcolepsy had been receiving psychostimulants for several years and were older (average age: 56.9 years and 49.5 years, disease duration: 30.6 years and 21.8 years, respectively) compared to participants of the present study. As reported earlier, effects of both of age [24] and medication [25] should be considered when interpreting DTI results.

Several studies have reported an amygdala dysfunction in narcolepsy-cataplexy[26,27]. In the canine model of narcolepsy, neurodegeneration with gliosis was found in the amygdala[28], and abnormal activity of amygdala neurons was suggested to be related to the occurrence of cataplexy [29]. ADC values represent a tissue water diffusivity and a high ADC value may reflect several conditions due to vasogenic edema associated with increased extracellular space [13]. ADC values are also known to reflect changes in the histopathologic progression; i.e., a low ADC value indicates the presence of cytotoxic edema and cell injury leading to inflamation and cell death, and a high ADC value reflects necrosis, degeneration, and demyelination [30]. Recently, a study on human subjects fond that a high ADC value also represented compensatory gliosis due to vasogenic edema [31], and another study, using an animal model, reported associated of a high ADC value with gliosis following hypoxia-induced ischemia [32]. Similar to previous reports using different techniques [26,27], our study showed some microstructural abnormalities (high ADC value) in the left amygdala in the NA/CA group, and no changes the NA w/o CA group. The left amygdala has been suggested to play a role in emotional interference resolution by processing arousing verbal stimuli, while the right amygdala processes non-verbal stimuli [33]. Considering these previous suggestions, we think that our result of microstructural abnormalities in the left amygdala might be associated with compensatory hyperactivities in the right amygdala, as reported by Schwartz S et al [27].

A previous VBM study indicated gray matter volume reduction in the inferior frontal gyrus in narcolepsy with cataplexy, and the authors speculated that hypocretin neuron loss might lead to some degree of cortical neuroglial atrophy and cortical volume loss [34]. In contrast, our results showed a higher ADC value for the right inferior frontal gyrus. Although the reasons for such differences remain unclear, differences in treatment and disease duration between the 2 studies should be considered. Regarding this, although the NA/CA participants in our study were younger (29.4+/−4.9 years old) than those in the study by Kaufmann et al. [34] (36.9+/−5.8 years old), we did not find any significant correlations between the neuroimaging findings, disease duration, and age at onset of narcolepsy. Kaufmann et al. [34] also reported that the volume reduction in the gray matter was independent of disease duration. The influence of medication, mainly antidepressants and psychostimulants, taken for years in their study [34], may have affected the neuroimaging results of loss of cortical volume in contrast to our study.

In the present study, the NA/CA and NA w/o CA groups showed morphological differences; the 2 groups differed in the ADC values for the right inferior frontal gyrus and FA values for the right precuneus. Although it is still debatable, Thannickal et al. reported decreased hypocretin fiber density throughout the hypothalamus in narcolepsy with cataplexy and partial (33%) loss of hypocretin cells in the posterior hypothalamus in narcolepsy without cataplexy [12]. These findings suggest that symptomatic differences between narcolepsy with and without cataplexy are related to either the severity and localizations of hypocretin neurons loss or a different pathway. Since hypocretin neuron projections are widely distributed over the CNS, including the cerebral cortex [35], cerebral cortex abnormalities in the NA/CA group observed in our study might be related to hypocretin neuron loss. If that is the case, then the lack of any morphological abnormalities in the cortex in the NA w/o CA group suggests the absence of, or perhaps limited, hypocretin cell loss. Recently, Bayard et al. reported slower performance and more variable results on simple reaction time tasks for patients having narcolepsy with cataplexy compared to those having narcolepsy without cataplexy [36]. Some studies have suggested that the right inferior frontal gyrus plays a predominant role in executive control [37], and the precuneus as well as the dorsolateral prefrontal cortex, is associated with executive control of attention shifts [38]. Thus, the right inferior frontal gyrus and the right precuneus abnormalities, along with a modest change in the executive network area, identified in the present study, may reflect the attention dysfunction in NA/CA. Our findings also favor the notion that cataplexy is related to abnormal interactions between the amygdala, post-central gyrus (Brodmann area 3), which is associated with motor control, and inferior frontal gyrus, which is associated with the production of emotions, since abnormal FA and ADC values in these areas were observed only in the NA/CA group.

Previous studies reported milder severity of EDS, lower REM propensity and less disturbed nocturnal sleep in patients having narcolepsy without cataplexy than those having narcolepsy with cataplexy [10,11]. Short sleep latencies and multiple SOREMPs on the MSLT, suggesting a narcolepsy-like phenotype, may be observed in several conditions, including shift-work disorder and behaviorally induced insufficient sleep syndrome, as well as in cases of obstructive sleep apnea syndrome, low nocturnal oxygen saturation, and antidepressant drug intake [39,40]. Altogether, these findings favor that narcolepsy without cataplexy is not a homogeneous entity, unlike narcolepsy with cataplexy which may be also an unstable and reversible condition. Accordingly, we failed to find any neuroimaging differences between the NA w/o CA and NC groups.

This study has several limitations. First, we did not measure CSF-hypocretin-1 levels in the patients. However, we assume that almost all patients with typical sporadic NA/CA were hypocretin deficient, while 80–90% of the patients with a long disease history of NA w/o CA had normal CSF-hypocretin-1 levels [9]. Thus, we hypothesize that brain morphological differences noted between the NA/CA and NA w/o CA groups relate to hypothalamic hypocretin dysfunction. Second, the duration of disease in both patients groups was over 10 years on average, so potential morphological abnormalities observed in this study might involve compensatory changes that had occurred in response to the basic pathology of narcolepsy. Third, similar to previous neuroimaging studies, the present study recruited relatively few patients in the NA/CA and NA w/o CA groups, which may cause a type I error, possibly contributing to some conflicting results between studies.

In summary, our study has demonstrated that brain morphometric abnormalities in the left amygdala, left inferior frontal gyrus, and left postcentral gyrus exist in narcolepsy with cataplexy, but not in narcolepsy without cataplexy. These findings suggest that these 2 types of narcolepsy have different pathological mechanisms. Further studies are needed to investigate the cause of neuronal alterations in the brain areas involved in narcolepsy with cataplexy and to validate the absence of neuroimaging biomarkers in narcolepsy without cataplexy.

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Author Contributions

Conceived and designed the experiments: MN YD YI. Performed the experiments: MN. Analyzed the data: MN. Contributed reagents/materials/analysis tools: SN KH YU. Wrote the paper: MN.

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Electroencephalographic Findings Related With Mild Cognitive Impairment in Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Taeko Sasai, MT, PhD[1,2,3,4]; Masato Matsuura, MD, PhD[4]; Yuichi Inoue, MD, PhD[1,2,3]

[1]Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan; [2]Yoyogi Sleep Disorder Clinic, Tokyo, Japan; [3]Department of Somnology, Tokyo Medical University, Tokyo, Japan; [4]Department of Life Sciences and Bioinformatics, Division of Biomedical Laboratory Sciences, Graduate School of Health Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Study Objectives: Mild cognitive impairment (MCI) and electroencephalographic (EEG) slowing have been reported as common findings of idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) and α-synucleinopathies. The objective of this study is to clarify the relation between MCI and physiological markers in iRBD.

Design: Cross-sectional study.

Setting: Yoyogi Sleep Disorder Center.

Patients or Participants: Thirty-one patients with iRBD including 17 younger patients with iRBD (younger than 70 y) and 17 control patients for the younger patients with iRBD.

Interventions: N/A

Measurements and Results: Montreal Cognitive Assessment (MoCA) and n-polysomnogram (PSG) were conducted of all participants. In patients with iRBD, the factors associated with MCI were explored among parameters of REM sleep without atonia (RWA), score of Sniffin' Sticks Test (threshold-discrimination-identification [TDI] score), RBD morbidity, and RBD severity evaluated with the Japanese version of the RBD questionnaire (RBDQ-JP). The younger iRBD group showed significantly lower alpha power during wake and lower MoCA score than the age-matched control group. MCI was detected in 13 of 17 patients (76.5%) on MoCA in this group. Among patients wtih iRBD, the MoCA score negatively correlated with age, proportion of slow wave sleep, TDI score, and EEG spectral power. Multiple regression analysis provided the following equation: MoCA score = 50.871–0.116*age -5.307*log (δ power during REM sleep) + 0.086*TDI score (R^2 = 0.598, P < 0.01). The standardized partial regression coefficients were -0.558 for age, -0.491 for log (δ power during REM sleep), and 0.357 for TDI score (F = 9.900, P < 0.001).

Conclusions: Electroencephalographic slowing, especially during rapid eye movement sleep and olfactory dysfunction, was revealed to be associated with cognitive decline in idiopathic rapid eye movement sleep behavior disorder.

Keywords: Electroencephalogram, Lewy body disease, mild cognitive impairment, Parkinson disease, REM sleep behavior disorder

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INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dream-enacting behaviors during REM sleep associated with increased muscle activity in submentalis or limb muscle.[1] Several previous reports have described that a certain number of patients with RBD progress to α-synucleinopathies such as Parkinson disease (PD) and dementia with Lewy bodies (DLB).[2-5]

Mild cognitive impairment (MCI) frequently occurs in PD as a nonmotor symptom of the disorder, even in the early stage of the disease.[6] In patients with RBD, some studies have identified MCI such as deficits in attention, executive functions, and visuospatial abilities as a marker of neurodegeneration.[7,8]

During the past decade, studies using quantitative electroencephalographic (EEG) analysis have revealed EEG slowing as manifesting a cortical dysfunction in patients with idiopathic rapid eye movement sleep behavior disorder (iRBD).[9,10] In addition, EEG slowing on polysomnogram (PSG) has been reported as a candidate early marker of the development of MCI in patients with the disorder.[11]

To date, no report in the relevant literature has presented an assessment in which clinical or EEG variables of RBD are actually associated with MCI in the disorder. This study was conducted to clarify the association between descriptive RBD variables or the EEG spectral power variables and cognitive findings.

METHODS

Patients and Measurements

The Ethical Committee of the Neuropsychiatric Research Institute approved this study. Written informed consent was obtained from all participants. In this study, 31 patients with iRBD were enrolled (67.0 ± 7.5 y, male:female = 24:7). The patient group was divided into two groups by median value of age: (1) younger patients with iRBD (younger than 70 y) and (2) older patients with iRBD (70 y or older). We set the control group age and sex-matched with the younger iRBD group without cognitive complaint and without sleep complaints in whom RBD was excluded completely using PSGs.

All patients with iRBD underwent PSGs and Sniffin' Sticks Testing shortly after the first visit (within 2 w). The control group underwent PSGs without undergoing Sniffin' Sticks Testing. All these patients self-rated the Japanese version of the Epworth Sleepiness Scale[12] at the first visit. According to

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Address correspondence to: Yuichi Inoue, MD, PhD, Japan Somnology Center, Neuropsychiatric Research Institute, 1-24-6 Yoyogi, Shibuya-ku, Tokyo, Japan; Tel: +81-3-3374-2016; Fax: +81-3-3374-2038; E-mail: inoue@somnology.com