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ORIGINAL ARTICLE

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How Do Restless Legs Syndrome Patients Recognize Daytime Sleepiness? - The Multiple Sleep Latency Test -

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Background and Objective Restless legs syndrome induces sleep fragmentation and impairs sleep quality. Although insomnia is the most frequently reported symptom, a substantial proportion of patients report excessive daytime sleepiness (EDS), and the factors that contribute to EDS need to be assessed for optimal treatment.

Methods Sixty-five untreated idiopathic restless legs syndrome (RLS) patients underwent polysomnography (PSG), multiple sleep latency test (MSLT) and the suggested immobilization test (SIT). After excluding nine patients with more than two sleep onset REM (SOREM) in the MSLT, and 15 patients with an apnea-hypopnea index of ≥ 10/hr, 41 patients were finally included. The severity of EDS was evaluated using the Epworth sleepiness scale (ESS), and the severity of RLS by International RLS Study Group Rating Scale (IRLS), and SIT. RLS patients were sub-grouped into sleepy RLS (S-RLS) (ESS > 10), and non-sleepy RLS (NS-RLS) (ESS ≤ 10).

Results The mean age upon evaluation was 54.56 ± 11.91 years of age (female: 70.7%), and the duration of RLS before diagnosis was 11.87 ± 10.65 years. RLS patients had decreased sleep efficiency, increased arousal indexs, increased periodic limb movements during sleep (PLMS) index, and movement arousal index (MAI) by PSG. There were nine patients (22%) in the S-RLS group, and 32 patients (78%) in the NS-RLS group. IRLS severity was significantly higher in the S-RLS than in the NS-RLS group ($p = 0.023$). The seven patients with SOREM had a mean REM latency of 2.81 ± 5.4. Correlation analysis revealed a negative correlation between the MSLT mean sleep latency and the PLMS index ($p = 0.003$, $\rho = 0.463$) and MAI ($p = 0.040$, $\rho = 0.334$).

Conclusions EDS is frequent in RLS-PLMS patients and subjective sleepiness was found to be higher in patients that reported severe RLS symptoms.

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Key Words Restless legs syndrome, Daytime sleepiness, Multiple sleep latency test.

INTRODUCTION

Restless legs syndrome (RLS) is a disorder characterized by uncomfortable dysesthesias or paresthesias in the legs that occurs primarily while resting at night and is alleviated by movement. The prevalence of this disorder is about 10% in Europe and the United States.[1,2] One study has reported a prevalence of RLS in 7.5% of the adult Korean population.[3] About 80% of RLS patients have periodic limb movements during sleep (PLMS).[4] The sensory symptoms and motor symptoms of RLS and PLMS often disrupt sleep and impair sleep quality, and the most common sleep related symptom in RLS is insomnia, which has a reported rate among RLS patients of 58 to 95%.[4,5] However, few studies have addressed excessive daytime sleepiness (EDS) in RLS patients, and few epidemiological studies have reported on the risk of increased daytime sleepiness [Epworth sleepiness scale (ESS) > 10 or > 11] in subjects with RLS compared to normal control patients.[6-9] One meta analysis based study revealed that 29.6% of RLS subjects had an ESS score of > 10, with an average score of 8.4 ± 4.8.[10] Other studies have been undertaken to objectively identify daytime sleepiness by the multiple sleep latency test (MSLT) study, and these have reported short sleep latencies for RLS patients with daytime sleepiness.[11-13] The aim of the present study was to assess the EDS and MSLT findings of idiopathic RLS patients, and to identify factors related to daytime sleepiness in untreated RLS patients.

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METHODS

Patient Selection

From August 2008 to September 2009, we retrospectively reviewed 154 untreated idiopathic RLS patients. Patients were eligible for inclusion in this study if they met the diagnosis criteria of RLS according to the International Classification of the Sleep Disorder-II criteria,[14] and completed polysomnography (PSG), the MSLT, and suggested immobilization test (SIT). Medical records were reviewed and questionnaires were evaluated to exclude any other sleep disorders capable of causing daytime sleepiness, such as, sleep-disordered breathing, narcolepsy, idiopathic hypersomnia, circadian rhythm disorders, chronic sleep deprivation, insomnia, the use of sedative medication, and major systemic, neurologic, and psychiatric disorders. Patients were excluded if the MSLT results indicated more than two sleep onset REM (SOREM), which is suggestive of a co-morbid cause of hypersomnia, and when a PSG result suggested an apnea-hypopnea index (AHI) ≥ 10/hr.

Clinical Assessments

The subjective severity of RLS symptoms were evaluated using the International RLS Study Group Rating Scale (IRLS)[15] and subjective daytime sleepiness were evaluated using the ESS.[16] The IRLS scale consists of 10 questions concerning symptoms and the impact of symptoms on daily activities and mood. Preset answers to questions were scored from 0 to 4 points, where 0 represented the absence of a problem and 4 represented a severe problem. The ESS questionnaire requires subjects to rate the likelihood that they might doze off or fall asleep in eight different everyday situations. The sleepiness is scored from 0 to 3 points, where 3 represent a high likelihood of dozing or falling asleep.

PSG was conducted using a six channel EEG, a two channel EOG, a four channel EMG for chin, intercostals muscles, right and left anterior tibialis, and EKG (Embla Co., Broomfield, CO, USA). Sleep stages, arousals, apneas/hypopneas, respiratory effort related arousals, and periodic limb movement were analyzed manually according to the American Academy of Sleep Medicine criteria.[17] The Severity of RLS was documented using the SIT[18] before the night of PSG, and the EDS was evaluated using the MSLT[19] after the PSG night. The SIT proceded as the patients were seated on a bed in a reclining (45 degrees) position with both feet outstretched. The test lasted for 60 minutes and the subjective low extremity discomfort was recorded every five minutes. The MSLT was conducted as the patients underwent five 30 min trial naps every two hours (from 9 am to 6 pm) in a dark room. The mean sleep latency (mean time to fall asleep) and number of sleep-onset REM sleep (REM sleep appearing within 15 min after sleep onset) were documented.

Clinical Measurement

Each questionnaire measurement was categorized according to the symptom severity or test results. According to the ESS questionnaire, an ESS > 10 was defined as sleepy and ESS ≤ 10 as non-sleepy groups. The subjective severities of RLS were defined as mild, moderate and severe according to the IRLS scale 1 to 10, 11 to 20, and > 21 respectively. The SIT was scaled from 0 to 100, the higher number indicates more severe symptoms. A cut-off score of 10 was used to describe the severity of the average leg discomfort as determined by the mean leg discomfort score (MDS).

Statistical Analysis

Continuous data are expressed as means (±SDs), and categorical data as frequencies and percentages. To test for trends in baseline characteristics, Pearson's Chi-square test was used to analyze categorical variables and the Mann-Whitney test was used for continuous variables. Correlation analysis was performed using Spearman's correlation coefficients. Statistical significance was accepted for two-tailed p values of < 0.05. The analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 125 untreated idiopathic RLS patients, 65 completed full PSG, MSLT, and SIT evaluations. Twenty-four patients were excluded; nine patients with > 2 SOREM in the MSLT, and 15 patients with an AHI of ≥ 10/hr. Finally, 41 patients were included in this study. Twenty-nine (70.7%) of the 41 patients were female, with the mean patient age upon evaluation as 54.56 ± 11.91 years, and the duration of RLS before diagnosis was 11.87 ± 10.65 years. The PSG results revealed a decrease in sleep efficiency, and an increase in the arousal index, wakefulness after sleep onset, periodic limb movements during sleep (PLMS), and movement arousal index (MAI). The mean sleep latency was within the normal range. The subjective severities of RLS symptoms were scaled by the IRLS questionnaire; 24.4% reported mild, 19.5% moderate, and 46.3% severe symptoms. The PLMS index ranged from 0 to 155, and 80.5% had a PLMS index of > 5/hr (mean PLMS index: 28.41 ± 33.63/hr). The mean MAI was 4.55 ± 5.87/hr. The main de-mographics and PSG, SIT, and MSLT results are summarized in Table 1.

Patients were classified into two groups according to the ESS scores. Sleepy RLS (S-RLS) patients [n = 9 (22%)] were defined as having an ESS of > 10, and non-sleepy RLS (NS-RLS) patients [n = 32 (78%)] were defined as having an ESS of ≤ 10. Clinical histories and PSG, MSLT, and SIT results of these two groups were compared. Differences between the S-RLS and NS-RLS were only significant for IRLS (p = 0.023). This result revealed that patients in the S-RLS group had a higher score in the IRLS

Table 1. Patient demographics and the PSG, SIT, and MSLT results

	Total	S-RLS	NS-RLS	p-value
Number of patients	41	9 (22.0%)	32 (78%)	
Female (n, %)	29 (70.7)	6 (66.7)	23 (71.9)	
Age (mean ± SD, yr)	54.56 ± 11.91	49.44 ± 16.63	56.00 ± 10.09	0.195
Duration of RLS (mean ± SD, yr)	11.87 ± 10.65	9.44 ± 8.72	12.31 ± 10.90	0.676
ESS	7.51 ± 4.37	13.56 ± 2.88	5.81 ± 2.98	
IRLS	22.34 ± 8.06	27.67 ± 6.52	20.84 ± 7.89	0.023
Normal (n, %)	4 (9.8)			
Mild (n, %)	10 (24.4)			
Moderate (n, %)	8 (19.5)			
Severe (n,%)	19 (46.3)			
PSG results				
Time in bed (min)	549.16 ± 61.24	488.90 ± 49.62	450.79 ± 62.25	0.120
Total sleep time (min)	378.24 ± 60.41	395.00 ± 46.93	373.53 ± 63.53	0.069
Sleep efficiency (%)	82.52 ± 8.48	80.84 ± 6.46	82.98 ± 9.01	0.511
Sleep latency (min)	16.20 ± 19.42	16.41 ± 15.20	16.14 ± 20.66	0.722
AI (/hr)	17.60 ± 7.59	20.29 ± 7.85	16.84 ± 7.47	0.195
PLMS index (/hr)	28.41 ± 33.63	23.97 ± 23.85	25.23 ± 35.47	0.745
MAI (/hr)	4.55 ± 5.87	4.53 ± 4.48	4.27 ± 6.19	0.525
Sleep architecture				
N1 stage (%)	16.38 ± 8.06	18.33 ± 7.26	15.83 ± 8.30	0.327
N2 stage (%)	55.26 ± 11.75	54.13 ± 8.63	55.58 ± 12.59	0.749
N3 stage (%)	7.17 ± 7.44	7.13 ± 10.33	7.18 ± 6.62	0.609
REM stage (%)	21.11 ± 8.46	20.42 ± 6.04	21.31 ± 9.09	0.816
WASO (min)	64.72 ± 36.22	77.50 ± 28.36	61.13 ± 37.74	0.235
WASO (%)	21.52 ± 34.63	16.96 ± 6.14	22.80 ± 39.11	0.410
MSLT results				
Mean sleep latency (min)	10.20 ± 6.27	10.19 ± 6.51	9.18 ± 5.71	0.657
SOREM 1 (n)	7	1	6	0.591
REM latency in SOREM (min)	2.81 ± 5.4	1.33 ± 4.00	2.70 ± 5.38	0.676
SIT				
MDS	26.40 ± 23.28	38.59 ± 33.36	22.97 ± 18.90	0.327
MDS > 10 (n, %)	31 (75.6)	6 (66.7)	21 (65.6)	0.954

RLS: restless legs syndrome, S-RLS: sleepy RLS, NS-RLS: non-sleepy RLS, PSG: polysomnography, AI: arousal index, PLMS: periodic limb movement in sleep, MAI: movement arousal index, WASO: wakefulness after sleep onset, MSLT: multiple sleep latency test, SIT: suggested immobilization test, MDS: mean leg discomfort score, ESS: Epworth sleepiness scale, IRSL: international RLS study group rating scale, SOREM: sleep onset REM, REM: rapid eye movement.

questionnaire, which means more severe subjective RLS symptoms. Variables found to be non-significant were; sex, age, duration of RLS, PSG, and MSLT (Table 1). Correlation analysis showed that IRLS and ESS were positively correlated ($\rho = +0.432$, $p = 0.005$) (Table 2A).

All patients underwent the MSLT. Three patients failed to fall asleep in five nap trials; mean sleep latencies (mSL) were taken as 20 minutes for these cases. The mSL of enrolled patients was 10.20 ± 6.27 minutes. Seven patients had SOREM, and only one patient was in the S-RLS group and six patients were in the NS-RLS group. The mean REM latency of seven SOREM episodes in these seven patients decreased to 2.81 ± 5.4 minutes. The individual study results of these seven patients are summarized in Table 3. No negative correlation was found between the ESS and MSLT mSL in both the S-RLS and NS-RLS groups. On the other hand, the PLMS index was found to be moderately negatively correlated with the MSLT mSL, and MAI was found to be moderately negatively correlated with the MSLT mSL

(PLMS: ρ = 0.463, MAI: ρ = 0.334) (Table 2B), which indicates that as PLMS index or MAI increases, the MSLT mSL decreases.

A positive SIT test was defined as a MDS > 10, which was observed in 65.9% of the patients (mean ± SD: 36.40 ± 23.28, range 0 to 91.10). The MDS was not found to be significantly associated with the EDS or the MSLT mSL.

DISCUSSION

The existence of excessive daytime sleepiness in RLS patients was evaluated by the ESS score [mean ESS score: 7.51 ± 4.37, range 0-19, ESS > 10 (22.0%)]. This result is in line with previous studies on daytime sleepiness in RLS patients, which have reported that 24-30% of RLS patients have an ESS of > 10.[5,9] The significance of this finding is that without adequate assessment, and through patient history, the EDS can be easily neglected.

In the present study, we focused on the assessment of daytime sleepiness in RLS patients, and we found that a subjective report of the EDS as ESS is positively related with the RLS severity as determined using the IRLS questionnaire. The MSLT findings in the enrolled patients revealed borderline decreases in mean sleep latency, and the SOREM was detected in seven patients. While the ESS and IRLS are questionnaire based on the self report of subjective symptom severity, they had poor correlations with objective evidence regarding the daytime sleepiness conducted by the MSLT.

One study reported that patients with a primary complaint of insomnia and/or PLMS showed no correlation between the PLMS index or arousal index and daytime sleepiness as measured by the MSLT.[13] This study enrolled PLMS patients, and demonstrated a poor correlation between the EDS and sleep efficiency or daytime sleepiness as measured by the MSLT. However, one other study reported a negative correlation between the sleep efficiency at night and the mean sleep latency as determined by the MSLT, and no correlation was found between the PLMS index and MSLT mSL.[11]

In the present study, the mean sleep latency by the MSLT was found to be negatively related to the PLMS index and MAI. This result indicates that the factor that influences sleep latency, as determined by the MSLT, is related more to the nocturnal disturbance by the PLMS, rather than the RLS severity. This finding indicates that subjective sleepiness in RLS patients is poorly correlated with PSG parameters, such as, total sleep time and sleep efficiency, or with the MSLT mSL and SOREM. However, a significant correlation in the severity of RLS symptoms, which indicates that these patients might recall the disturbances they experienced at night as sleepiness during the day. On the other hand, actual daytime sleepiness was found to be more related to the PLMS symptoms and movement arousals.

Although our study has not identified the fact that rather the daytime sleepiness should be focus on the subjective or objective of sleepy state, and alleviation of RLS-PLMS symptoms will improve daytime sleepiness. We suggest that symptomatic

Table 2. Spearman's correlation coefficients between the PLMS index and MSLT mSL, MAI, and mSL

	ρ	p-value
A. Correlation between EDS and RLS severity		
IRLS	+0.432	0.005
B. Correlation between MSLT mSL and PLMS and MAI		
PLMS	-0.463	0.003
MAI	-0.334	0.040

EDS: excessive daytime sleepiness, IRLS: international RLS study group rating scale, MSLT: mean sleep latency test, mSL: mean sleep latency, PLMS: periodic limb movement in sleep, MAI: movement arousal index, RLS: restless legs syndrome.

Table 3. Summarized results of seven patients with SOREM according to the MSLT study

Patients	ESS	PSG					MSLT	
		TST (min)	SL (min)	REM (%)	PLMS index (/hr)	MAI (/hr)	mSL (min)	REM latency (min)
S-RLS								
1	17	396.5	6.5	24.0	11	9	2.8	12
NS-RLS								
2	4	460	8.5	19	21	20	6.3	11.5
3	8	419	2.5	30.8	26	2	12	10.1
4	2	385.5	12.5	27.1	90	17	4	12
5	0	395.0	31.0	51.6	0	0	18.1	11
6	2	380	3.0	27.2	28	5	5.1	11.5
7	2	393.5	12.7	19.8	0	0	2.0	11

S-RLS: sleepy RLS, NS-RLS: non-sleepy RLS, PSG: polysomnography, MSLT: multiple sleep latency test, PLMS: periodic limb movement in sleep, MAI: movement arousal index, TST: total sleep time, SL: sleep latency, ESS: Epworth sleepiness scale, RLS: restless legs syndrome, SOREM: sleep onset REM, REM: rapid eye movement.

treatment of RLS and PLMS may improve daytime sleepiness.

Conflicts of Interest

The authors have no financial conflicts of interest.

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