

The Correlation between Clinical Variables and Sleep Onset Rapid Eye Movement Period Frequencies in Narcoleptic Patients

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Background and Objective A diagnosis of narcolepsy is defined by less than 8 minutes of mean sleep latency, and two or more sleep onset rapid eye movement periods on the Multiple Sleep Latency Test. This study examined the relationship between the sleep onset rapid eye movement period frequencies during Multiple Sleep Latency Test and narcoleptic symptom severity.

Methods From March 2004 to August 2009, 126 patients suffering from excessive daytime sleepiness who visited the Sleep Disorders Clinic of St. Vincent's Hospital at the Catholic University of Korea were tested by polysomnography and Multiple Sleep Latency Test. Subjects were divided into three groups according to the number of sleep onset rapid eye movement periods that appeared on the Multiple Sleep Latency Test. Symptom severity instruments included the Epworth Sleepiness Scale and the Stanford Center for Narcolepsy Sleep Inventory, and various sleep parameters. In addition, we performed human leukocyte antigen genotyping for human leukocyte antigen-DQB1*0602 on all patients.

Results Among the three groups classified by the number of sleep onset rapid eye movement periods during Multiple Sleep Latency Test, we found no significant differences in demographic features, Epworth Sleepiness Scale, and most polysomnographic findings. However, we observed cataplexy, hypnagogic hallucination, sleep paralysis, and human leukocyte antigen-DQB1*0602 positivity more frequently in groups with higher sleep onset rapid eye movement period frequencies. In addition, the proportions of stage II sleep, REM sleep latency from polysomnography, and mean sleep latency and mean REM sleep latency from the Multiple Sleep Latency Test significantly decreased with increasing sleep onset rapid eye movement period frequency.

Conclusions In this study, we demonstrated that sleep onset rapid eye movement period frequency during Multiple Sleep Latency Test correlated with sleep architecture, daytime symptom severity, and frequency of human leukocyte antigen-DQB1*0602 positivity in narcolepsy. Further studies are needed to explore the pathophysiology of narcolepsy associated with sleep onset rapid eye movement periods.

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Key Words Narcolepsy, Sleep onset rapid eye movement periods, Cataplexy, Sleep paralysis, Hypnagogic hallucination.

INTRODUCTION

Narcolepsy occurs in 0.02-0.18% of individuals in their late teens and early twenties regardless of gender.¹ The main symptoms of narcolepsy are excessive daytime sleepiness; cataplexy, which is a sudden involuntary decrease in muscle tension in various areas of body (in response to laugh, excitement, anger, or other emotional changes); abnormal changes in REM sleep period such as sleep paralysis; and hypnagogic or hypnopompic hallucinations.²⁻⁵ These symptoms affect various aspects of the narcoleptic patient's life, including vocation, education, ability to drive, and interpersonal relationships, leading to a decline in quality of life comparable to that of patients with epileptic or major depressive disorders.⁶

The etiology of narcolepsy is unknown, but recent studies suggest that decreased secretion of hypocretin, a critical hormone in the maintenance of arousal, is strongly associated. Genetic studies have found human leukocyte antigen (HLA)-DR2 and HLA-DQB1*0602 to be the most

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distinct indicator of narcolepsy in all human ethnicities.⁷⁻¹⁰

Nocturnal polysomnography and the Multiple Sleep Latency Test (MSLT) provide an objective measure of excessive daytime sleepiness, and the presence of REM sleep is used to diagnose narcolepsy.¹¹ Confirming narcolepsy without cataplexy requires a positive MSLT, a mean sleep latency (MSL) of ≤ 8 minutes, and two or more sleep onset rapid eye movement periods (SOREMPs).¹² According to previous reports, the sensitivity and specificity of using two or more SOREMPs in the MSLT to diagnosis of narcolepsy is 78% and 93%, respectively.¹³⁻¹⁷

Despite of being one of the pathognomonic features of narcolepsy, clinicians have confined the use of SOREMP to diagnosing narcolepsy via the MSLT, and no study has previously examined the relationship between the SOREMP numbers and narcolepsy severity. Watson, et al.¹⁸ found a linear relationship between HLA-DQB1*0602 frequency and daytime sleepiness as defined by the Epworth Sleepiness Scale (ESS), narcolepsy severity as defined by Ullanlinna Narcolepsy Scale, age of symptom onset, and sleep latency (SL). Jiménez-Correa, et al.¹⁹ proved a positive correlation between ESS,²⁰ and sleep paralysis and diurnal tiredness, but failed to clarify any relationship between MSLT results and the severity of sleep paralysis, cataplexy or hypnagogic hallucinations.

In this study, we divided 126 narcoleptic patients into three groups according to the number of SOREMPs that appeared during MSLT, and investigated their clinical features and the prevalence of HLA-DQB1*0602 to define the relationship between SOREMP frequency and narcoleptic symptom severity.

METHODS

Subjects

From March 2004 to August 2009, patients who were suspected of having narcolepsy, based on diagnostic criteria for the International Classification of Sleep Disorders,²¹ were selected among individuals reporting excessive daytime sleepiness. Polysomnography and MSLT were performed in the Sleep Disorders Clinic of St. Vincent's Hospital at The Catholic University of Korea. All patients with a chief complaint of sleep apnea or periodic limb movement, suggesting other sleep disorders, were excluded. Patients with a serious medical illness, a seizure disorder, evidence of definite neurological deficit, history of substance or alcohol abuse, or other psychiatric illness that may affect sleep were excluded as well, leaving 126 participants for further evaluation. This study was approved by the institutional review board of the St. Vincent's Hospital at The Catholic University of Korea. Informed consent was obtained according to the Declaration of Helsinki.

Assessment of Symptom Severity

All participants were interviewed by psychiatrists who had

completed the sleep medicine course to assess narcoleptic symptoms. Data, including the frequency of excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucination, and the characteristics of cataplexy, were collected through a structured interview. Participants were also asked to complete a written questionnaire. The questionnaire was composed of the Stanford Center for Narcolepsy Sleep Inventory²² and contained 146 questions including ones concerning triggering factors, location, duration, frequency of cataplexy, and the ESS, which is a useful screening tool of excessive daytime sleepiness.

Sleep Laboratory Tests

All participants underwent nocturnal polysomnography and subsequent MSLT.

The polysomnography room was soundproof, lightproof, and equipped with a television and air conditioning facility to make patients feel at ease during the test. Polysomnography lasted 8 hours, adjusted to accustomed sleep hours of each patient, between 9 PM to 9 AM the next morning. We performed electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG) on lower limbs and chin, and measured participants' oronasal airflow, chest movement, abdominal movement, and blood oxygen saturation. For EEG, we placed unipolar electrodes on C3, O1/A2 to determine the sleep stages. For EOG, we placed unipolar electrodes 1 cm above each participant's left lateral canthus and 1 cm below the right lateral canthus for differentiation of slow and rapid eye movements. We recorded axial muscle tone in the submentalis muscle under the chin, and took EMG recording from the tibialis anterior muscles in both legs to detect periodic limb movements and other abnormal motor activity during sleep. To record the participants' breathing sounds, we placed a microphone around larynx and pulse oxymeter on the right index finger. The recording rate was 10 mm/sec, the calibration voltage was 5 mm/50 μ V, and we used a high pass filter of 53 Hz.

To ensure that participants had at least 6 hours of sleep prior to the test and no other causes for excessive daytime sleepiness were present, we performed each participant's MSLT during the day immediately following the polysomnography. The MSLT consisted of five nap trials separated by 2-hour intervals at 9 AM, 11 AM, 1 PM, 3 PM, and 5 PM. We recorded each participant's EEG, EOG, EMG, and electrocardiography (ECG) in the same way as we did the polysomnography.

Each nap trial allowed the participant 20 minutes in which to fall asleep. If the participant achieved sleep within the allotted time, we allowed them to sleep for 15 minutes while examining the recording for evidence of REM sleep. If we observed more than two SOREMPs during the first four trials, we omitted fifth. Caffeinated beverages that can affect sleep or arousal were prohibited for the entire duration of the test. We also instructed the participants to stay awake between nap trials, and ensured this by having a polysomnographic technician moni-

tor the participants. The sleep initiation and stage were confirmed manually, according to the sleep stage scoring system proposed by Rech-tschaffen and Kales²³ measuring time in bed (TIB), sleep period time (SPT), total sleep time (TST), sleep efficiency index (SEI), the fractions of total awake time (TWT), total stage I sleep (TS1), total stage II sleep (TS2), total REM sleep (TREM), SL, and REM sleep latency (REML).

The primary parameters were MSL and the number of SOREMPs, which we defined as appearance of REM sleep during the first 15 minutes from sleep initiation. We defined two or more SOREMPs in combination with an MSL of ≤ 8 minutes as narcolepsy. We divided the participants into three groups according to the number of SOREMPs appeared during their MSLT: SOREMP 2 group, SOREMP 3 group, and SOREMP 4 group.

HLA Genotyping

First, we isolated lymphocytes from each participant's blood (2×10^6 cells/mL), added 0.5 mL polymerase chain reaction (PCR)-K buffer (1 mL $10 \times$ PCR buffer, 40 μ L NP-40, 45 μ L Tween-20, 30 μ L proteinase K (20 mg/mL), and 8.8 mL D/W), dissolved the cells at 58°C for 60 minutes, and raised the temperature to 95°C for 10 minutes to inactivate proteinase K before DNA was extracted. To determine the HLA-DQB1*0602 allele, we labeled allele-specific probes with Dig-11-dUTP using terminal transferase, dropped each sample onto a nylon membrane, and hybridized Dig-11-dUTP-labeled allele-specific probe with each sample on the membrane. We then assessed the gene expression using an anti-DIG antibody, and finally determined the genotypes.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 10, SPSS Inc., Chicago, IL, USA). We presented demographic data, clinical symptom frequencies, results of polysomnography and MSLT, and the HLA-DQB1 allele frequencies as

mean \pm standard deviation or as a percentage. To analyze demographic variables and data from the polysomnography and MSLT, we used the one-way ANOVA. We analyzed cataplexy, hypnagogic hallucination, sleep paralysis, and HLA-DQB1*0602 via the Chi-square test, regarding any p-value less than 5% as statistically significant.

RESULTS

Demographic Characteristics

Among the 126 participants who underwent MSLT, 32 (25.4%) had two SOREMPs, 43 (34.1%) had three SOREMPs, and 51 (40.5%) had four SOREMPs. In the SOREMP 2 group, 24 participants were male and 8 were female. Their mean age was 28.4 ± 15.4 , and the mean body mass index (BMI) was 26.1 ± 11.0 kg/m². In the SOREMP 3 group, 27 were male and 16 were female. The mean age was 31.3 ± 14.0 , and the mean BMI was 24.7 ± 4.3 kg/m². In the SOREMP 4 group, there were 35 males and 16 females. The mean age was 29.8 ± 14.4 , and the mean BMI was 24.3 ± 5.0 kg/m². The mean illness duration was 13.1 ± 13.9 years for the SOREMP 2 group, 12.3 ± 10.6 years for the SOREMP 3 group, and 12.9 ± 8.8 years for the SOREMP 4 group. No significant differences were observed in the demographic variables between the three groups (Table 1).

Clinical Symptoms

Mean scores of the ESS were 13.2 ± 5.1 in the SOREMP 2 group, 14.1 ± 5.1 in the SOREMP 3 group, and 15.1 ± 4.7 in the SOREMP 4 group. The numbers of participants in the SOREMP 2 group who had experienced cataplexy, hypnagogic hallucination, or sleep paralysis were 10 (43.5%), 11 (42.3%), and 5 (26.3%), respectively. In the SOREMP 3 group, 19 (61.3%) reported having cataplexy, 26 (81.3%) experienced hypnagogic hallucination, and 15 (51.7%) had sleep paralysis. In SOREMP 4 group, 34 (77.3%)

Table 1. Demographic and clinical symptoms in narcoleptic patients classified according to the number of sleep onset rapid eye movement periods (SOREMPs)

	SOREMP 2 (n = 32)	SOREMP 3 (n = 43)	SOREMP 4 (n = 51)
Demographic data			
Age*	28.4 \pm 15.4	31.3 \pm 14.0	29.8 \pm 14.4
Male (%)*	75.0	62.8	68.6
BMI (kg/m ²)*	26.1 \pm 11.0	24.7 \pm 4.3	24.3 \pm 5.0
Disease duration*	13.1 \pm 13.9	12.3 \pm 10.6	12.9 \pm 8.8
Clinical symptoms			
ESS*	13.2 \pm 5.1	14.1 \pm 5.1	15.1 \pm 4.7
Cataplexy No.(%)†	10 (43.5)	19 (61.3)	34 (77.3)
Hypnagogic hallucination No.(%)†	11 (42.3)	26 (81.3)	39 (84.8)
Paralysis No.(%)†	5 (26.3)	15 (51.7)	27 (65.9)

*Not statistically significant among three groups. †p < 0.0001 by Chi-square test. BMI: body mass index, ESS: Epworth Sleepiness Scale.

Table 2. Comparison of polysomnographic findings, MSLT data, and HLA-DQB1*0602 expression in narcoleptic patients classified according to the number of sleep onset rapid eye movement periods (SOREMPs)

	SOREMP 2 (n = 32)	SOREMP 3 (n = 43)	SOREMP 4 (n = 51)	p-value
Polysomnographic data				
TIB (min.)	457.5 ± 31.1	455.2 ± 27.7	449.4 ± 30.1	0.487
SPT (min.)	2111.5 ± 8784.6	440.3 ± 63.0	446.2 ± 31.1	0.247
TST (min.)	427.5 ± 39.1	427.4 ± 42.3	408.0 ± 63.2	0.163
SEI	93.9 ± 5.4	94.2 ± 7.3	91.0 ± 12.3	0.246
Stage I sleep (%)	8.3 ± 5.7	9.4 ± 4.8	10.7 ± 6.9	0.234
Stage II sleep (%)	56.6 ± 8.8	54.2 ± 9.1	49.1 ± 10.9	0.005*
SWS (%)	14.7 ± 23.2	10.4 ± 7.4	10.8 ± 6.9	0.375
TREM (%)	19.3 ± 5.0	20.2 ± 5.4	20.6 ± 8.9	0.743
TWT (%)	5.4 ± 5.4	5.5 ± 7.3	8.3 ± 12.3	0.302
SL (min.)	5.6 ± 8.5	3.6 ± 3.7	3.3 ± 3.7	0.191
REML (min.)	82.8 ± 50.7	49.4 ± 46.7	22.6 ± 37.9	0.000*
SOREMPs	2.9 ± 0.9	3.0 ± 1.0	3.3 ± 0.8	0.107
MSLT data				
Mean SL (min.)	5.3 ± 2.9	2.4 ± 1.4	1.3 ± 0.7	0.000*
Mean RL (min.)	9.3 ± 2.5	3.3 ± 1.2	2.0 ± 1.4	0.000*
HLA-DQB1*0602 positive (%)	42.3	81.3	84.8	< 0.0001*

*p < 0.05 by ANOVA or Chi-square test.

TIB: time in bed, SPT: sleep period time, TST: total sleep time, SEI: sleep efficiency index, SWS: slow wave sleep, TREM: total rapid eye movement (REM) sleep, TWT: total awake time, SL: sleep latency, REML: REM sleep latency, MSLT: multiple sleep latency test, RL: REM latency, HLA: human leukocyte antigen.

had experienced cataplexy, 39 (84.8%) reported hypnagogic hallucination, and 27 (65.9%) had sleep paralysis. Cataplexy, hypnagogic hallucination, and sleep paralysis occurred more frequently in the group with higher SOREM frequency during MSLT ($p < 0.0001$)(Table 1).

Polysomnography and Multiple Sleep Latency Test

Polysomnographic findings showed no significant differences in TST, SEI, TWT, TS1, TREM, SL among the three groups. However, the SOREM4 group had a significantly lower proportion of TS2 and REML. From the MSLT, we found the MSL was 5.3 ± 2.9 minutes for the SOREM 2 group, 2.4 ± 1.4 minutes for the SOREM 3 group, and 1.3 ± 0.7 minutes for the SOREM 4 group; these differences were statistically significant ($p < 0.001$). The mean REML in the MSLT was 9.3 ± 2.5 minutes for the SOREM 2 group, 3.3 ± 1.2 minutes for the SOREM 3 group, and 2.0 ± 1.4 minutes for the SOREM 4 group. Mean REML in MSLT tended to decrease as SOREM frequencies increased, and this correlation was statistically significant ($p = 0.000$)(Table 2).

HLA-DQB1*0602

Among the 126 narcoleptic patients, 78 (61.9%) had HLA-DQB1*0602. Furthermore, HLA-DQB1*0602 appeared at a significantly greater frequency as SOREM frequency increased. There were 11 (42.3%) participants with the gene in the SO-

REM 2 group, 28 (81.3%) in the SOREM 3 group, and 39 (84.8%) in the SOREM 4 group ($p < 0.0001$)(Table 2).

DISCUSSION

In this study, we found that patients with higher numbers of SOREMps during the MSLT experienced more narcoleptic symptoms such as cataplexy, hypnagogic hallucination, and sleep paralysis. A previous study by Hong, et al.²⁴ found that patients with narcolepsy with cataplexy show higher numbers of SOREMps than narcolepsy patients without cataplexy. The results of the current study can be understood in the same context.

Previous studies also reported that narcoleptic patients with cataplexy experience hypnagogic hallucination and sleep paralysis more frequently than those who have narcolepsy without cataplexy, suggesting that the presence of cataplexy can be a predictor of narcoleptic symptom severity.^{25,26} However, cataplexy has its limits as a predictor because narcoleptic patients usually experience cataplexy several months to years after they first complain of excessive daytime sleepiness, and it takes more than 10 years for cataplexy to appear in 10-15% of patients.²⁷ This study suggests that frequent SOREMps during the MSLT predicts the more severe and homogenous phenotype of narcolepsy. And this result implies that MSLT is useful, not only to diagnose narcolepsy, but also to predict the clinical symptom se-

verity of patients complaining of excessive daytime sleepiness.

Rogers, et al.²⁸ reported significant diminution of SEI, SL, REML when SOREMP. Our study showed no significant difference in SEI and SL among the three groups, but REML significantly decreased as SOREMP frequency increased. And Our narcoleptic patients, also shared other features common to narcolepsy, such as reduced sleep stage 2.²⁹ These results suggest that the number of SOREMPs reflects the pathophysiology and sleep architecture of narcolepsy.

Previous reports also found HLA-DQB1*0602 positivity to be higher in narcoleptic patients with cataplexy.^{18,25,26} We found that HLA-DQB1*0602 positivity was higher in groups with more SOREMPs, suggesting that SOREMP frequency is also a significant marker for narcolepsy along with cataplexy and HLA-DQB1*0602 positivity.

Continuous researches on the predictor of severity of narcoleptic symptoms, such as cataplexy or HLA-DQB1*0602 positivity, is in progress. Here we demonstrated the association between the number of SOREMPs appearing in the MSLT and the severity or frequency of narcoleptic symptoms, supporting the idea that SOREMP frequency could be used as one of the predictors of narcoleptic symptom severity.

Despite our interesting results, this study was limited by the absence of data from a normal control group, varying group sizes, and a lack of information on some participants' narcoleptic symptoms. Supplementary studies on the predictors of narcolepsy severity are needed to further elucidate the pathophysiology and etiology of narcolepsy.

In conclusion, we demonstrated the association between the number of SOREMPs during the MSLT and sleep architecture, severity of daytime symptoms, and frequency of HLA-DQB1*0602 positivity in narcolepsy. This suggests that SOREMP frequency during the MSLT and narcoleptic symptoms have a phenotypic overlap, and that further studies can discover the pathophysiology of narcolepsy associated with SOREMPs.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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