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Clinical and Polysomnographic Comparison between Narcolepsy without Cataplexy and Idiopathic Hypersomnia

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Background and Objective The aim of this study is to compare the clinical, electrophysiological (Polysomnography, PSG; Multiple Sleep Latency Test, MSLT) and biological data (HLA DQB1*0602 typing) in idiopathic hypersomnia with narcolepsy without cataplexy.

Methods 80 patients with narcolepsy without cataplexy and 71 patients with idiopathic hypersomnia without a long sleep time were recruited at the Sleep Center of St. Vincent's Hospital. MSLT data and PSG findings from the time of their diagnosis were reviewed. HLA typing was performed.

Results Results indicated that the idiopathic hypersomnia group showed a significant longer mean sleep latency in MSLT compared with the narcolepsy without cataplexy group. But there was no significant difference in the Epworth Sleepiness Scale (ESS) scores between the two groups. Although HLA positivity of both groups was not statistically significant ($p = 0.065$), HLA positivity tended to be higher in the narcolepsy without cataplexy group than the idiopathic hypersomnia group. The number of awakenings was slightly higher in the idiopathic hypersomnia group, but there was no statistical significance. The number of spontaneous arousal and total arousal indices was not significantly different between the groups. For the PSG, the idiopathic hypersomnia group showed a significantly longer sleep latency than the narcolepsy without cataplexy group ($p = 0.009$). REM sleep latency (REML) was significantly shorter in the narcolepsy without cataplexy group compared to the idiopathic hypersomnia group. The percentage of REM (SREM) was significantly higher in the narcolepsy without cataplexy group, and the percentage of the wake time during sleep period (SWT) was significantly lower in the narcolepsy without cataplexy group.

Conclusions There were no significant differences of subjective sleep measures such as ESS, disturbed nocturnal sleep, number of naps, age of onset of hypnagogic hallucination, and age of onset of sleep paralysis between patients with narcolepsy without cataplexy and idiopathic hypersomnia. So, the use of objective tests such as the PSG and MSLT may be inevitable for the differential diagnosis of narcolepsy without cataplexy from idiopathic hypersomnia.

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Key Words Narcolepsy, Cataplexy, Idiopathic hypersomnia, HLA.

INTRODUCTION

Many patients report symptoms of hypersomnia with mostly excessive daytime sleepiness. According to the second edition of the International Classification of Sleep Disorders (ICSD-2), hypersomnias of central origin are categorized as narcolepsy and idiopathic hypersomnia (IH).[1] And narcolepsy can be divided into two categories based on the existence of cataplexy as narcolepsy with cataplexy (NTC) and narcolepsy without cataplexy (NATC).

The symptoms of narcolepsy including abnormal sleep tendencies such as excessive daytime sleepiness (EDS), disturbed nocturnal sleep, sleep paralysis and hypnopompic or hypnagogic hallucinations can occur in any person who is severely sleep deprived, and only cataplexy is unique to narcolepsy.[2]

Narcolepsy with cataplexy can be diagnosed easier than other hypersomnia of central origin. But narcolepsy without cataplexy can be more complicated for the diagnosis and the differential diagnosis from idiopathic hypersomnia because it only manifests EDS subjectively

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and does not report other pathognomic findings.

Cataplexy alone, if typical, is thus sufficient to diagnose narcolepsy. But in narcolepsy without cataplexy, the MSLT and polysomnography (PSG) tests are needed to confirm the diagnosis. A positive MSLT [Mean Sleep Latency (MSL) ≤ 8 minutes and 2 or more sleep onset rapid eye movement periods (SOREMPs)] must be recorded for a diagnosis of narcolepsy without cataplexy. And then the residual patients with unexplained daytime sleepiness, no cataplexy, and abnormally short sleep latency but without 2 SOREMPs are classified as having idiopathic hypersomnia.[3,4]

According to the literature, it has been reported that idiopathic hypersomnia is one of the most controversial diagnoses in the clinical practice of sleep medicine.[5] Although frequent awakenings and poor quality of nocturnal sleep are well-known characteristics of narcolepsy with cataplexy, there has been limited data about the characteristics of idiopathic hypersomnia and narcolepsy without cataplexy.[6]

Short but refreshing naps of narcolepsy patients will be helpful to differentiate narcolepsy from idiopathic hypersomnia. However idiopathic hypersomnia has non-specific clinical features and confirmatory electrophysiological findings.

Idiopathic hypersomnia can be diagnosed by the exclusion of any other known cause of excessive daytime sleepiness.[7] Therefore, MSLT and PSG should be done for the differential diagnosis of both disorders.

The aim of this study is to find out the clinical, electrophysiological and biological differences between narcolepsy without cataplexy and idiopathic hypersomnia.

METHODS

Patients

All patients provided written informed consent for this study which was approved by the Institutional Review Board. The patients' chief complaint for visiting our institution was excessive daytime sleepiness. They were evaluated and diagnosed for sleep disorder in the sleep laboratory, Department of Psychiatry, St. Vincent's Hospital, The Catholic University of Korea, Suwon, Korea, over a 10-year period from 2002-2011.

The exclusion of sleep apnea as the major cause of daytime sleepiness was decided clinically (snoring and breathing pauses, demographic data, severity, nature, and onset of sleepiness, and the presence of other symptoms such as dissociated REM sleep events) and on the basis of the nocturnal PSG results, as described in the ICSD-2, and patients were excluded if their pre-MSLT nocturnal sleep time was less than 6 hours and/or if they had periodic limb movements during sleep, or circadian rhythm sleep disorders.[3,8]

Patients were separated into diagnostic groupings based on the ICSD-2 revised classification after performing nocturnal PSG and MSLT. This categorization resulted in the following groupings: 1) narcolepsy without cataplexy (n = 80, nocturnal PSG performed and AHI ≤ 5; MSLT with MSL ≤ 8 and ≥ 2 SOREMPs); 2) idiopathic hypersomnia cases without a long sleep time (n = 71, nocturnal PSG AHI ≤ 5, MSLT with MSL ≤ 8, and 0 or 1 SOREMPs).

Polysomnographic and Multiple Sleep Latency Test Findings

Polysomnography and MSLT were performed using standard systems (Embla). The following items were recorded during the PSG: 4-channel scalp electroencephalography (C3-A2, C4-A1, O1-A2, and O2-A1), 2-channelelectro-oculography, electromyography of the mandibular muscles, electrocardiography, snoring sensor measurements, oral and nasal airflow, chest and abdominal respiratory effort, electromyography of the tibialis anterior muscle, and percutaneous oxygen saturation measurement. In terms of the sleep stage scoring, newer criteria have been published.[9] However, in order to use data that were collected before the publication of the new criteria, we used the criteria suggested by Rechtschaffen and Kale, in the present study.[10] Electroencephalographic arousals and periodic limb movements during sleep were assessed based on the criteria of the American Sleep Disorders Association Atlas Task Force, 1992, 1993. Respiratory events were assessed based on the Chicago criteria (American Academy of Sleep Medicine Task Force, 1999).

Sleep onset rapid eye movement periods during PSG was defined as a period of REM sleep occurring within 20 minutes after the onset of sleep. MSLT was performed four times every 2 hours (i.e., at 10:00, 12:00,14:00, and 16:00) according to the standard protocol.[11] In the present study, a fifth MSLT session was not required in any of the narcolepsy cases because we were able to make the diagnosis based on the results of four MSLT sessions. Sleep latency on the MSLT was defined as the time from lights out to the first epoch when either sleep stage appeared. SOREMP during MSLT was defined as a period of REM sleep occurring within 15 min after sleep onset. For MSLT measurements, the mean sleep latency, REM latency and mean rate of SOREMP appearances per total number of sessions were compared among the two groups.[6]

HLA-DQB1*0602 Typing

Blood samples were collected and sent to Stanford University for HLA typing. DNA was extracted using the standard procedure and DQB1 typing was performed using a combination of techniques, including polymerase chain reaction, sequence-specific primer amplification and sequencing of allele-specific products.[12] All blood samples were also studied for the DQB1*0602-specific codon using the previously described polymerase chain reaction sequence-specific primer method. In this report, only the presence or absence of DQB1*0602 was reported. We com-

pared the PSG, MSLT findings and HLA DQB1*0602 positivity rate between the two different groups, retrospectively based on the electronic medical records.[3]

Data and Statistical Analysis

Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). The independent-sample t-test and Mann-Whitney U test were used to compare the MSLT and PSG parameters between the two groups. The chi-square test was used to compare the differences in categorical variables. A p value of < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Findings of Patients

The patients' demographic and clinical parameters for each group are presented in Table 1. The mean age was 29.13 ± 12.72 in the IH group and 25.68 ± 11.98 in the NATC group. The BMI was 22.09 ± 2.96 in the IH group and 22.88 ± 3.39 in the NATC group. The Epworth Sleepiness Scale Score was 12.76 ± 4.78 in the IH group and 13.52 ± 4.74 in the NATC group. There were no significant differences between the two groups in age, BMI and ESS scores. Duration of illness was defined as the time spent from the onset of symptoms to the diagnosis. Both groups showed no significant difference in duration of illness. The duration of illness was 8.31 ± 9.19 in the IH group and 8.04 ± 7.93 in the NATC group.

Males were statistically more frequent in the narcolepsy without cataplexy group. The number of episodes of disturbed nocturnal sleep was 1.37 ± 1.34 in the IH group and 1.84 ± 2.44 in the NATC group. The number of naps was 4.73 ± 3.94 in the IH group and 4.59 ± 3.26 in the NATC group. The age of onset of hypnagogic hallucination was 19.33 ± 7.07 in the IH group and 16.19 ± 8.59 in the NATC group. The age of onset of sleep paralysis was 18.83 ± 3.29 in the IH group and 18.83 ± 5.62 in the NATC group. The existence of sleep paralysis was 14/59 (28.8%) in the IH group and 14/42 (33.3%) in the NATC group. The existence of hypnagogic hallucination was 14/40 (35%) in the IH group and 10/40 (25%) in the NATC group. The subjective sleep measures such as disturbed nocturnal sleep, number of naps, age of onset of sleep paralysis, the age of onset of hypnagogic hallucinations, the existence of sleep paralysis and existence of sleep hallucination did not show any statistically significant differences between the two groups.

Although HLA positivity of both groups was not statistically significant ($p = 0.065$), HLA positivity tended to be higher in the NATC group than the IH group. Of 71 patents with idiopathic hypersomnia, 20 patients were HLA positive, and of 80 patients with narcolepsy without cataplexy, 33 patents were HLA positive. The percentage of HLA positive patients in the two groups was 28.2% for IH and 41.3% for NATC.

Multiple Sleep Latency Test Findings

The MSLT findings between the two groups are presented in Table 2. On MSLT, there was a significant difference in mean sleep latency between the two groups. The idiopathic hypersomnia group showed a significantly longer mean sleep latency compared to the narcolepsy without cataplexy groups (5.08 ± 1.71 min in the IH group vs. 3.20 ± 1.84 min in the NATC group, $p < 0.001$).

The number of SOREM was 0.37 ± 0.49 for IH and 2.91 ± 0.88 for NATC. This difference was statistically significant (< 0.001).

Table 1. Demographic and clinical findings between narcolepsy without cataplexy and idiopathic hypersomnia patients

	Narcolepsy without cataplexy (n = 80)	Idiopathic hypersomnia (n = 71)	p-value
Sex (M/F)	61/19	35/36	0.001*
Age	25.68 ± 11.98	29.13 ± 12.72	0.086
Duration of illness (yr)	8.04 ± 7.93	8.31 ± 9.19	0.863
BMI (kg/m^2)	22.88 ± 3.39	22.09 ± 2.96	0.140
ESS	13.52 ± 4.74	12.76 ± 4.78	0.447
Number of disturbed nocturnal sleep	1.84 ± 2.44	1.37 ± 1.34	0.936
Number of naps	4.59 ± 3.26	4.73 ± 3.94	0.989
Onset age of hypnagogic hallucination (yr)	16.19 ± 8.59	19.33 ± 7.07	0.232
Onset age of sleep paralysis (yr)	18.83 ± 5.62	18.83 ± 3.29	0.393
Sleep paralysis (%)	33.30	28.80	0.393
Hypnagogic hallucination (%)	25.00	35.00	0.232
HLADQB1*0602 (+) (%)	41.30	28.20	0.065

Analyzed by chi-square test, independent-sample t-test & Mann-Whitney U test.
*Statistically significant.
BMI: Body Mass Index, ESS: Epworth Sleepiness Scale, HLADQB1: Human Leukocyte Antigen DQB1.

Polysomnographic Findings

The polysomnographic findings between the two groups are presented in Table 3. Total sleep time (TST) was similar in the two groups (430.10 ± 50.83 min. in IH vs. 442.22 ± 38.26 min. in NATC, p = 0.164). Sleep efficiency was 92.68 ± 9.73% in IH and 90.50 ± 5.19% in NATC without significant difference between the two groups (p = 0.209). Sleep latency was significantly longer in the IH group (10.31 ± 17.26 min.) than the NATC group (8.21 ± 15.58 min. p = 0.009). REM latency from the onset of sleep (REML) was significantly shorter in the NATC group (119.15 ± 67.81 min. in IH vs. 74.61 ± 58.36 min. in NATC, p < 0.001).

The percentage of REM was significantly higher in the NATC groups (20.54 ± 5.61%) than the IH group (18.34 ± 6.57%, p = 0.042). In detail, patients whose REML was less than 20 minutes were zero (0%) in the IH group, while 20 patients (28.16%) had such a REML in the NATC group.

The percentage of wake time during the sleep period was 6.44 ± 9.64% in the IH group and 3.36 ± 4.39% in the NATC group.

The percentage of sleep stage 1 was 6.85 ± 9.22% in the IH group and 6.75 ± 7.03% in the NATC group. The percentage of sleep stage 2 was 54.34 ± 12.02% in the IH group and 54.33 ± 8.75% in the NATC group. The percentage of sleep stages 3 and 4 was 15.25 ± 10.11% in the IH group and 15.10 ± 9.42% in the NATC group.

There were no significant differences in the percentages of sleep stages between the two groups [Stage 1 (%), p = 0.857;

Table 2. Multiple sleep latency test findings between narcolepsy without cataplexy and idiopathic hypersomnia patients

	Narcolepsy without cataplexy (n = 80)	Idiopathic hypersomnia (n = 71)	p-value
Mean sleep latency	3.20 ± 1.84	5.08 ± 1.71	< 0.001*
Number of SOREM	2.91 ± 0.88	0.37 ± 0.49	< 0.001*

Analyzed by independent-sample t-test & Mann-Whitney U test.
*Statistically significant.
SOREM: sleep onset rapid eye movement.

Table 3. Polysomnographic findings between narcolepsy without cataplexy and idiopathic hypersomnia patients

	Narcolepsy without cataplexy (n = 80)	Idiopathic hypersomnia (n = 71)	p-value
Total sleep time (min)	442.22 ± 38.26	430.10 ± 50.83	0.164
Sleep latency (min)	8.21 ± 15.58	10.31 ± 17.26	0.009*
Sleep efficiency (%)	95.50 ± 5.19	92.68 ± 9.73	0.209
REML (min)	74.61 ± 58.36	119.15 ± 67.81	< 0.001*
REML < 20 min (%)	28.16	0	< 0.001*
REM (%)	20.54 ± 5.61	18.34 ± 6.57	0.042*
Wake time (%)	3.36 ± 4.39	6.44 ± 9.64	0.143
Sleep stage 1 (%)	6.75 ± 7.03	6.85 ± 9.22	0.857
Sleep stage 2 (%)	54.33 ± 8.75	54.34 ± 12.02	0.995
Sleep stages 3 and 4 (%)	15.10 ± 9.42	15.25 ± 10.11	0.799
Number of awakenings	3.84 ± 4.85	4.48 ± 7.80	0.742
Spontaneous arousal number	50.73 ± 22.81	47.74 ± 23.93	0.670
Total arousal number	57.98 ± 30.90	52.15 ± 29.44	0.232
Total arousal index	7.88 ± 4.55	7.48 ± 4.01	0.618
PLMI	2.53 ± 8.53	1.52 ± 5.16	0.669
PLMA	3.08 ± 7.44	1.75 ± 4.52	0.164
Apnea index	0.16 ± 0.47	0.16 ± 0.44	0.408
Hypopnea index	0.57 ± 0.79	0.99 ± 1.33	0.227

Analyzed by independent-sample t-test & Mann-Whitney U test.
*Statistically significant.
REML: REM latency from sleep onset, PLMI: periodic limb movement index, PLMA: periodic limb movement arousal index, REM (%): REM out of total sleep time, Wake time (%): wake time out of total sleep time, Stage 1 (%): percentage of each stage of sleep expressed as a ratio to TST, 2 (%): percentage of each stage of sleep expressed as a ratio to TST, 3 and 4 (%): percentage of each stage of sleep expressed as a ratio to TST.

Stage 2 (%), p = 0.995; Stages 3 and 4 (%), p = 0.799].

The number of awakenings was 4.48 ± 7.80 in the IH group and 3.84 ± 4.85 in the NATC group.

The arousal parameters such as the spontaneous arousal number, total arousal number and total arousal index were 47.74 ± 23.92, 52.15 ± 29.44 and 7.48 ± 4.01 respectively in the IH group, and 50.73 ± 22.81, 57.98 ± 30.90 and 7.88 ± 4.55 in the NATC group. Arousal parameters showed no statistical significances between the groups.

The apnea index was 0.16 ± 0.44 in the IH group and 0.16 ± 0.47 in the NACT group. The hypopnea index was 0.99 ± 1.33 in the IH group and 0.57 ± 0.79 in the NATC group.

DISCUSSION

The main differential finding between narcolepsy without cataplexy and idiopathic hypersomnia is the appearance of SOREM during MSLT. The number of SOREM of narcolepsy without cataplexy and idiopathic hypersomnia was 2.91 and 0.37 respectively. In most cases, it is hard to differentiate these two disorders by evaluating subjective symptoms. ESS represents a subjective symptom of EDS. However, there was no difference of the ESS score between the two groups.

We were also able to confirm the results of a previous study that showed that the idiopathic hypersomnia group had a significantly longer mean sleep latency on MSLT compared with the narcolepsy without cataplexy groups.[3]

In the present study, there was a significant difference in the sleep latency in MSLT between the two groups, but not in the ESS scores. These results could suggest that sleep latency on MSLT does not necessarily reflect subjective sleepiness as the number of SOREM does.[14] In addition, based on the previous study's results on patients with severe hypersomnia, it is possible that patients who have been exposed to severe hypersomnia for a long period can underestimate their sleepiness.[6,15-17]

Furthermore, the disturbed nocturnal sleep and number of naps as subjective parameters for sleep quality also have shown no statistical significance. This is proper evidence that the MSLT and PSG tests are necessary for the differential diagnosis of the two groups.

We also found that a surprisingly high percentage of narcolepsy subjects without cataplexy were male (76.3%). The percentage was comparable with that in idiopathic hypersomnia (49.3%). It is similar to the results of a previous study results in which the cases of diagnosed narcolepsy without cataplexy were found to be more prevalent in males. And it is possible that a high number of male subjects in the general population have mild symptoms consistent with narcolepsy without cataplexy.[3,18-20]

Short REM latency during nocturnal polysomnography was reported to be a highly predictive finding for diagnosing narcolepsy regardless of the presence of cataplexy.[21] In this study, the average REM latency of narcolepsy without cataplexy and idiopathic hypersomnia was 74.61 minutes and 119.15 minutes respectively. 28.16% of NATC had a sleep onset of REM of less than 20 minutes. However none of the patients in the IH group had SOREM during polysomnography.

We found that idiopathic hypersomnia showed a trend of a higher number of awakenings and the percentage of wake time during PSG. This finding seemed to be correlated with nocturnal sleep disturbance as a main symptom of narcolepsy. We may need more investigations about this finding.

In this study, we found a higher percentage of HLA positivity in idiopathic hypersomnia than in another study (28.2% vs. 20%). As HLA typing can be supportive of the diagnosis of narcolepsy, we need to investigate this finding. 26 patients out of 71 idiopathic hypersomnia patients (data is not shown) recorded one SOREM during the MSLT. We suggest that some of the real narcolepsy patients could be included in the idiopathic hypersomnia group due to their false negative MSLT findings. One study reported that in the well-defined group of narcolepsy with cataplexy, the MSLT was not positive in 9% of the cases. The percentage of false negativity for the MSLT increased to 13.3% if the more conservative MSL cut-off point of < 5 minutes was used. Other studies reported very similar results.[3,22,23] One SOREM group showed a slightly higher percentage of HLA positivity than the none-SOREM group (30.8% vs. 26.7%).

There are several limitations to this study. First, we recruited patients from a single institution, and it is unclear whether the patients with narcolepsy without cataplexy or idiopathic hypersomnia are representative of general patient populations with these disorders. Second, we did not use healthy controls for the comparisons of the MSLT and PSG parameters in this study. Third, PSG was recorded for only a single night, possibly leading to the inclusion of first-night effects in our findings.[6,24]

In future studies, we would like to conduct comparisons including patients with hypersomnia and healthy controls using the same protocol. Moreover, performing repetitive MSLT for those who have one SOREM during MSLT may give us important information.

Finally, we would like to clarify the underlying cause of pathological sleepiness between narcolepsy and idiopathic hypersomnia.

Conflicts of Interest

The authors have no financial conflicts of interest.

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