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Original Article

# Differences in electroencephalographic findings among categories of narcolepsy-spectrum disorders

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ABSTRACT

*Objective:* To clarify the differences in quantitative electroencephalographic (EEG) measures and their relation to clinical symptoms among narcolepsy-spectrum disorders.
*Methods:* The enrolled patients were: 28 with narcolepsy with cataplexy (NA-CA); 16 with NA without cataplexy (NA w/o CA) and HLA-DRB1*1501/DQB1*0602 positive (NA w/o CA HLA+); 22 with NA w/o CA and HLA negative (NA w/o CA HLA–); and 22 with idiopathic hypersomnia without long sleep time (IHS w/o LST). Nocturnal polysomnography (n-PSG) and quantitative EEG evaluation, as well as the Multiple Sleep Latency test (MSLT), were conducted for all patients.
*Results:* Patients with NA-CA or NA w/o CA HLA+ showed lower alpha power, higher delta and theta power during wakefulness, and higher alpha and beta power during rapid eye movement (REM) sleep, compared to those with NA w/o CA HLA– or IHS w/o LST. The former two groups also showed lower sleep efficiency and a higher rate of positivity of REM-related symptoms than the other two groups.
*Conclusions:* In narcolepsy, the presence of cataplexy and HLA positivity are associated with EEG slowing during wakefulness and increased fast EEG activity during REM sleep, REM-related symptoms and disrupted nocturnal sleep in narcolepsy.



## 1. Introduction

According to the Second Edition of the International Classification of Sleep Disorders (ICSD-2) [1], diagnosis of narcolepsy without cataplexy (NA w/o CA) and idiopathic hypersomnia (IHS) can only be made when a patient has both of the following: subjective excessive daytime sleepiness occurring almost daily for at least three months, and a mean sleep latency of less than 8 min on the Multiple Sleep Latency Test (MSLT). Additionally, the presence of two or more sleep-onset rapid eye movement (REM) sleep periods (SOREMPs) on the MSLT, which reflects increased REM sleep propensity, is set as a cardinal item for the diagnosis of NA w/o CA, and one or fewer SOREMPs as that of IHS.

Human leukocyte antigen (HLA)-DRB1*1501/DQB1*0602 and lowered levels of hypocretin-1 in cerebrospinal fluid (CSF) (<110 pg/mL) are observed in more than 90% of patients with narcolepsy with cataplexy (NA-CA). These two markers being positive are highly specific to this disease category [2–7]. Regarding their clinical symptoms, REM-related symptoms, such as sleep paralysis (SP) and hypnagogic hallucination (HH) reflecting the NA-specific increased REM propensity, are also commonly observed in patients with NA-CA [8–11]. Furthermore, disrupted nocturnal sleep as a subjective complaint or nocturnal polysomnographic (n-PSG) findings are common among these patients [12–15].

Compared with NA-CA, the positive rates for the NA-specific clinical markers described above are lower in patients with NA w/o CA. Positivity for HLA-DRB1*1501/DQB1*0602 is lower than 40%, and prevalence of REM-related symptoms is estimated at 30–40% in NA w/o CA [2,3,8]. Previously, a report described that the presence of HLA-DRB1*1501/DQB1*0602 in NA w/o CA was associated with the severity of excessive daytime sleepiness or higher positivity for REM-related symptoms in NA w/o CA, and that patients with NA w/o CA and HLA negative (HLA–) had similar symptomatic characteristics to those of IHS w/o long sleep time (LST), which supports the inclusion of IHS w/o LST in the narcolepsy spectrum [8]. Regarding the macrostructure of nocturnal sleep, a previous study has revealed that sleep efficiency and the number of arousals differ among patients with NA-CA, NA w/o CA, and IHS w/o LST [16]. In contrast, previous results elucidating the microstructure of nocturnal sleep have been divergent [17,18]. No report in the relevant literature has described an association between the macrostructure and microstructure of nocturnal sleep among

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patients with narcolepsy-spectrum disorders, particularly addressing the positivity/negativity of HLA-DRB1*1501/DQB1*0602.

The present study was conducted to investigate the quantitative electroencephalographic (EEG) measures found on nocturnal polysomnography (n-PSG) among patients with narcolepsy-spectrum disorders, addressing the positivity/negativity of HLA-DRB1*1501/DQB1*0602.

## 2. Methods

### 2.1. Subjects

The Ethical Committee of the Neuropsychiatric Research Institute approved this study. Written informed consent was obtained from all participants. Eligible patients were those with hypersomnia, who first visited the outpatient clinic of the Japan Somnology Center between May 2003 and May 2008, and had never received treatment for hypersomnia. Those who met the following inclusion criteria were enrolled in this study: (1) diagnosed as NA-CA, NA w/o CA, or IHS w/o LST, based on clinical symptoms, n-PSG finding and the MSLT, according to the diagnostic criteria in the ICSD-2; and (2) free of psychostimulant medication and anticataplectic drugs when they underwent n-PSG and MSLT. During clinical interviews, board-certified sleep-disorder specialist physicians carefully confirmed the presence/absence of cataplexy; this was characterized by a sudden loss of bilateral muscle tone that was provoked by strong emotions such as laughter, anger, fear, and surprise [19]. Patients were asked to take sufficient sleep (at least 6 h at night) and not to have an irregular sleep–wake schedule during at least 2 weeks before the n-PSG. In order to exclude false positive of NA w/o CA or IHS w/o LST, some patients who were suspected of having circadian sleep–wake rhythm disorders or chronic sleep deprivation were asked to record their sleep–wake patterns by an actigraphy. From pre-examination interviews and available actigraphic data, patients with the following conditions were excluded: (1) averaged total sleep time within the two weeks before the n-PSG and/or total sleep time immediately before the MSLT of less than 6 h; (2) irregular sleep–wake pattern within the 2 weeks before the n-PSG; (3) taking a 30 min or longer nap within the 3 h before starting the n-PSG; (4) an apnea/hypopnea index (AHI) > 5/h and/or periodic limb movement index (PLMI) > 15/h on the n-PSG; (5) abnormal sleep–wake cycles or a shortage of nocturnal sleep, recognized in the sleep diaries; and (6) a history of medication for other disorders that can cause false-positive MSLT results. Consequently, the following patients were enrolled in this study: 28 with NA-CA, 16 with NA w/o CA HLA-positive, 22 with NA w/o CA HLA–, and 22 patients with IHS w/o LST.

### 2.2. Procedures

At the first visit, HLA typing was performed on all participants. Based on this, those with NA w/o CA were subdivided into two groups: those with a positive finding for HLA-DRB1*1501/DQB1*0602 (NA w/o CA HLA+) and those with a negative finding for HLA-DRB1*1501/DQB1*0602 (NA w/o CA HLA–).

For all subjects, the Epworth Sleepiness Scale (ESS) [20] was self-checked at the first visit. Furthermore, their clinical charts were reviewed to investigate the self-reported existence of REM-related symptoms (SP and HH).

Diagnostic PSGs were performed using a standard system (Alice4; Respironics Inc., Murrysville, PA, USA) including: four channels of scalp electroencephalographic data (C3/A2, C4/A1, O1/A2, O2/A1); two electrooculographs; submental electromyography; electrocardiography; nasal/oral airflow data; an oximetry sensor recording oxygen saturation ($SpO_2$) data; a microphone for detecting snoring sounds; chest/abdominal respiratory effort data; and bilateral anterior tibialis electromyography. Sleep stages were scored according to criteria set by Rechtschaffen and Kales [21]. The EEG arousal and PLMI were evaluated according to criteria set by the American Sleep Disorders Association [22,23]. Respiratory events were also evaluated according to The American Academy of Sleep Medicine Chicago criteria [24]. The REM sleep periods observed within 15 min from sleep onset on n-PSG were defined as SOREMPs [25].

The MSLT was performed on the day after n-PSG, according to the standard protocol [26]. A SOREMP was defined as the appearance of an epoch of REM sleep during the first 15 min of naps on the MSLT. The respective mean REM latencies of the three narcoleptic groups on the MSLT were compared after excluding the group with IHS w/o LST.

In either n-PSG or MSLT, sleep onset was defined when one or more 30-sec epochs of sleep occurred.

### 2.3. Quantitative electroencephalographic evaluation

The EEG samples during wake were collected before starting the PSG recordings. Before starting the n-PSG, in order to obtain EEG samples during wake, technicians instructed the participants to lie awake in bed keeping their eyes closed. The EEG samples during REM sleep were selected from all sections of clear REM sleep between two rapid eye movements [27]. All EEG samples during slow wave sleep (SWS) were selected from periods of stage N3 [28]. For all PSG data, a board-certified sleep technician carefully eliminated any recording artifacts. The EEG data were recorded with 500 Hz of sampling rate, 0.3 Hz of low-frequency filter, and 35 Hz of high-frequency filter. Quantitative EEG evaluation was performed blindly using fast Fourier transform (FFT) on the artifact-free periods during wake, REM sleep, and SWS [27]. The FFT on 2-s epochs (1024 points) yielding 0.448 Hz of spectral resolution was performed on C3/A2, C4/A1, O1/A2, and O2/A1 derivations using a computer program (CSA play analysis; Norpro Light Systems, Tokyo, Japan). Segment overlap was defined as 24 points (48 ms) in the next segment. The artifact rejection level was set as 300 μV. Frequency bands were as follows: alpha, 8.0–13.0 Hz; beta, 14.0–28.0 Hz; theta, 4.0–7.0 Hz; and delta, 0.5–3.0 Hz. The numbers of analyzed epochs were as follows: in NA-CA, 194 ± 47 epochs of REM sleep period, 99 ± 77 epochs of SWS, and 96 ± 85 epochs of wake period; in NA w/o CA HLA+, 196 ± 57 epochs of REM sleep period, 85 ± 53 epochs of SWS, and 77 ± 66 epochs of wake period; in NA w/o CA HLA–, 222 ± 58 epochs of REM sleep period, 78 ± 44 epochs of SWS, and 34 ± 39 epochs of wake period; in IHS w/o LST, 178 ± 53 epochs of REM sleep period, 69 ± 47 epochs of SWS, and 42 ± 33 epochs of wake period.

### 2.4. Statistical analysis

To test the normality and homogeneity of variances of the continuous variables, the Shapiro–Wilk test and Levene test were conducted. After checking the normality and equality of variances with a $p$-value greater than 0.05, analysis of variance (ANOVA) followed by Bonferroni's post-hoc test was conducted to compare age, clinical symptoms, MSLT measures and macrostructural measures, as well as EEG spectral power on n-PSG among the patient groups. Chi-squared tests were also used to compare the prevalence of REM-related symptoms among the groups. All statistical analyses were conducted using software (SPSS 17.0; SPSS Inc.), setting the significance level as 0.05.

## 3. Results

### 3.1. Demographic and multiple sleep latency test findings

Table 1 presents the demographic and MSLT findings of the participants (Table 1). Significant differences in the rates of people having REM-related symptoms were found among the four groups