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# Comparison of the clinical and electrophysiological characteristics between type 1 and type 2 narcolepsy: a cross-sectional study

Kuniyuki Niijima[1*] and Masakazu Wakai[1]

## Abstract

**Introduction** Narcolepsy is a chronic brain disease characterized by excessive sleepiness and classified into two types based on the presence of cataplexy or reduced level of cerebrospinal fluid orexin-A (hypocretine-1): narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). These two types differ in symptoms other than cataplexy, as well as in certain examination findings. The present study aimed to investigate the clinical and electrophysiological characteristics of NT1 by comparing its features with those of NT2.

**Methods** Subjects were 118 first diagnosed and untreated patients with narcolepsy. They underwent both polysomnography (PSG) and multiple sleep latency test (MSLT) as a sleep test. Diagnosis was established in accordance with International Classification of Sleep Disorders, Third Edition, and the type of narcolepsy was determined by the presence or absence of cataplexy, patients with cataplexy were diagnosed with NT1, and without cataplexy were diagnosed with NT2. We investigated characteristics of the patients, PSG and MSLT outcomes, and applied a suite of duly statistical analysis to account for each parameter.

**Results** Among the 118 subjects, 35 patients (29.7%) were NT1, and 83 patients (70.3%) were NT2. Excessive daytime sleepiness which was measured by Japanese version of Epworth sleepiness scale (JESS) was significantly higher in NT1 than NT2. Furthermore, the presence of sleep hallucination ($n=29$, 82.9%), sleep paralysis ($n=18$, 51.4%), difficult maintaining sleep ($n=22$, 62.9%), and sleep related movement and behavior disorders ($n=7$, 20.0%) were significantly higher in NT1 than those in NT2. Additionally, parameters indicative of sleep fragmentation, such as the arousal index and wake time after sleep onset measured in PSG, exhibited a statistically significant increase in NT1 when contrasted with NT2.

**Conclusions** Fragmentation of nocturnal sleep which is explained by the high arousal index and the long wake time after sleep onset on PSG was considered a characteristic finding of NT1 compared with NT2, and the patients with NT1 experienced greater difficulty of maintaining sleep. Concomitantly, the prevalence of NT1 in this study may be a representative value of the prevalence of NT1 among the patients with narcolepsy in Japan.

**Keywords** Narcolepsy type1, Narcolepsy type2, Sleep fragmentation, Difficult maintaining sleep, Prevalence

*Correspondence:
Kuniyuki Niijima
kniijima@chutoen-hp.shizuoka.jp
[1] Sleep Medicine Center, Chutoen General Medical Center, 1-1 Shobugaike, Kakegawa City, Shizuoka, Japan

## Introduction

Narcolepsy is a chronic brain disease that manifests itself as an excessive daytime sleepiness, concomitant with symptoms such as cataplexy, sleep hallucinations, and sleep paralysis (Bassetti et al. 2019). According to the International Classification of Sleep Disorders Third Edition (ICSD-3), and its Text Revision (ICSD-3-TR), the current diagnostic criteria, narcolepsy is divided into two different types: narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2) based on the presence of cataplexy or reduced level of cerebrospinal fluid orexin-A (hypocretine-1) (AASM 2014, 2023). Despite both types manifesting excessive sleepiness, symptoms other than cataplexy and some examination findings are dissimilar between the two types. Through an examination of our sleep medicine center's clinical results, we analyzed the clinical and electrophysiological characteristics of NT1 by comparing features with those of NT2.

## Methods

### Subjects

Subjects of investigation were one-hundred eighteen first diagnosed and untreated patients with narcolepsy who sought consultation at the Sleep Medicine Center of Chutoen General Medical Center from May 2013 to December 2021. They underwent both polysomnography (PSG) and multiple sleep latency test (MSLT) as a sleep test. Diagnosis was established in accordance with ICSD-3, based on two primary indicators: (1) excessive daytime sleepiness or fall asleep every day, for at least 3 months, (2) mean sleep latency $\leq$ 8 min on MSLT with $\geq$ 2 sleep onset rapid eye movement (REM) sleep period (SOREMP) or REM sleep latency $\leq$ 15 min on nocturnal PSG if the only one SOREMP on MSLT. We also confirmed several other criteria, including: 1) regular sleep-wake cycles for at least 2 weeks prior to testing as documented in sleep diaries, and exclusion of insufficient sleep (less than 7 h sleep), shift work, and other circadian rhythm sleep-wake disorders; 2) absence of effects from drugs or their metabolites, or discontinuation of such drugs; and 3) absence of any other sleep disorders or their successful management, as assessed by PSG performed on the night prior to MSLT. Patients with hypersomnia due to physical disorders, or those suspected of having such disorders, were excluded. The type of narcolepsy was determined by the presence or absence of cataplexy, patients with cataplexy were diagnosed with NT1, and without cataplexy were diagnosed with NT2.

This investigation was announced to the public on the website of our hospital and all patients could choose to participate or refuse to participate in this study. The Chutoen General Medical Center Clinical Research Ethics Committee approved this study (approval number: 1203220810).

### Demographic and clinical data

We investigated Age at diagnosis, Age at estimated symptom onset, the Japanese version of the Epworth Sleepiness Scale (JESS), and the presence of cataplexy, hypnagogic hallucinations, sleep paralysis, difficult maintaining sleep (DMS), and sleep-related movement and behavior disorders (SRMBD) as characteristics of the patients.

Furthermore, we conducted an examination of the following sleep-related parameters: Total sleep time (TST), Sleep latency (SL), Sleep efficiency (SE), Wake time after sleep onset (WASO), Arousal index (ArI), Apnea-hypopnea index (AHI), the presence of REM sleep without atonia (RWA), RWA index (RWAI), the presence of Periodic leg movement (PLM), PLM index (PLMI), the presence of Periodic leg movement associated with arousal (PLMAr), PLMAr index (PLMArI), and the presence of SOREMP on PSG. We also evaluated Mean sleep latency (MSL) and the frequency of SOREMP (F-SOREMP) on the MSLT.

In the assessment of RWA, we adhered to the scoring criteria outlined in the American Academy of Sleep Medicine (AASM) scoring manual Ver.2.0 or later. This scoring was based on the following definitions: (1) sustained muscle activity (tonic activity) during REM sleep, defined as an epoch of REM sleep with chin electromyogram amplitude exceeding the minimum amplitude observed in non-REM sleep for at least 50% of the epoch's duration; (2) excessive transient muscle activity (phasic activity) during REM sleep, involving the presence of bursts of transient muscle activity in at leaset 50% of ten sequential 3-s mini-epochs within a 30-s REM sleep epoch. The RWAI was calculated using the following formula: RWAI = (number of tonic REM epochs + number of phasic REM epochs) /number of total REM epochs.

### Statistical analyses

We conducted a comprehensive statistical analysis comparing various factors between NT1 and NT2, including Age at diagnosis, Age at estimated symptom onset, Diagnostic delay (calculated as Age at diagnosis minus Age at estimated symptom onset), JESS, PSG results (including TST, SL, SE, WASO, ArI, AHI, RWAI, PLMI, PLMArI), and MSLT results (MSL, and F-SOREMP). To analyze the data, we used the Mann-Whitney U test due to the relatively young age of onset of narcolepsy, the high JESS scores in patients with excessive sleepiness, and the non-normal distribution of each PSG or MSLT parameter. We used an analysis of co-variance (ANCOVA) to adjust the results for sex and age in the case of BMI. We used

chi-squared test for male-to-female ratio, the presence of each symptom, and the occurrence of SOREMP, RWA, PLM, and PLMAr on PSG. An alpha value was fixed at 0.05 for all statistical analyses carried out using the SPSS package (Ver. 29.0).

## Results

Among one-hundred and eighteen subjects (75 males), 35 patients (20 males) were NT1, comprising 29.7% of the total, while 83 patients (55 males) were NT2, comprising 70.3%. No significant difference in terms of sex distribution were found between NT1 and NT2 patients. Furthermore, both the median age at diagnosis and the median age at estimated symptom onset exhibited no statistically significant differences between the two groups, and there was no significant variation in the median diagnostic delay. The mean BMI was significantly higher in NT1 than NT2. Regarding symptoms, excessive daytime sleepiness as measured by the JESS, the presences of sleep hallucination, sleep paralysis, DMS, and SRMBD were significantly more prevalent in NT1 than in NT2 (Table 1).

The results of PSG are presented in Table 2. Patients with NT1 exhibited significantly higher ArI and WASO compared to patients with NT2. SE was significantly lower for NT1 than NT2. Furthermore, significant correlations between DMS and SE, WASO, and ArI were found only in ArI of NT1 (correlation coefficient was 0.345). The ArI of NT1 with DMS (15.55, IQR 12.73–24.88) was significantly higher than that of NT1 without DMS (10.30, IQR 7.45–16.75). Although there was no significant difference in the prevalence of nocturnal SOREMP, it was found in 40% of patients with NT1, which was higher than that of NT2 (24.1%). With regards to RWAI, PLMI, PLMArI, and their respective prevalence, no significant differences were identified; however, these values were higher in NT1 compared to NT2.

## Discussion

The present study investigated the characteristics of NT1 by comparing clinical and electrophysiological findings of NT1 with those of NT2. We found significantly severe sleepiness, as indicated by higher JESS scores, among individuals with NT1. And the prevalence of all of other symptoms such as hypnagogic hallucination, sleep paralysis, DMS, and SRMBD were also significantly higher in NT1. Excessive sleepiness, cataplexy, hypnagogic hallucination, and sleep paralysis are regarded as a tetrad of symptoms of narcolepsy (Murray and Foley 1974), which may occur due to a deficiency or reduction of orexin (cerebrospinal fluid orexin-A, also called hypocretin-1: ≦110 pg/mL) (Bassetti et al. 2019). Sleep instability is likely to arise in the setting of orexin insufficiency/deficiency (Tsujino and Sakurai 2013), leading to disrupted/disturbed nighttime sleep (Maski et al. 2022). Furthermore, the presence of a high ArI in PSG provides

**Table 1** Demographics and clinical characteristics of patients with isolated NT1 and NT2

| | NT1 ($n=35$) | NT2 ($n=83$) | *P*-value |
|---|---|---|---|
| Male sex | 20 (57.1) | 55 (66.3) | 0.347 |
| Age at diagnosis, year | 23.0 [18.0–30.0] | 21.0 [17.0–25.0] | 0.232 |
| Age at estimated symptom onset, year | 14.0 [11.0–17.0] | 16.0 [13.0–19.0] | 0.268 |
| Diagnostic delay[a], year | 7.0 [1.0–11.0] | 5.0 [2.0–8.0] | 0.242 |
| BMI | 23.75 ± 3.87 | 21.71 ± 3.82 | 0.010* |
| JESS score | 20.0 [14.0–23.0] | 16.0 [13.0–20.0] | 0.015* |
| Hypnagogic hallucination, yes | 29 (82.9) | 34 (41.0) | < 0.01* |
| Sleep paralysis, yes | 18 (51.4) | 25 (30.1) | 0.028* |
| DMS, yes | 22 (62.9) | 24 (28.9) | < 0.01* |
| SRMBD, yes | 7 (20.0) | 5 (6.0) | 0.022* |

Utilizing data extracted from our medical archives, we conducted a thorough examination of gender distribution, BMI, and symptomatic profiles of both NT1 and NT2. Statistical scrutiny was employed to discern any noteworthy disparities. Specifically, the Mann-Whitney test was deployed for the determination of medians, while an ANCOVA was leveraged to assess BMI, and the chi-square test was applied to categorical variables. Our investigation revealed statistically significant elevations in BMI as well as in the incidence of each individual symptom in the NT1 group, relative to NT2

Values are presented as median [interquartile range], n (%), or mean ± standard deviation

*NT* Narcolepsy type, *JESS* Japanese version of the Epworth sleepiness scale, *BMI* Body mass index, *DMS* Difficult maintaining sleep, *SRMBD* Sleep related movement and behavior disorders

Median [interquartile range] tested by Mann-Whitney U test

BMI tested by ANCOVA (covariance: age and sex)

n (%) tested by chi-square test

*$P < 0.05$

[a] Diagnostic delay = Age at diagnosis – Age at estimated symptom onset

**Table 2** Polysomnographic data of patients with isolated NT1 and NT2

| PSG parameters | NT1 ($n=35$) | NT2 ($n=83$) | *P*-value |
|---|---|---|---|
| TST, minutes | 498.80 [453.50–544.20] | 533.50 [471.50–597.20] | 0.056 |
| SL, minutes | 3.00 [1.00–6.00] | 2.50 [1.00–4.00] | 0.613 |
| SE, % | 88.50 [77.60–93.80] | 93.20 [86.10–95.20] | 0.021* |
| WASO, minutes | 72.00 [31.00–143.00] | 36.00 [24.50–86.00] | 0.018* |
| ArI | 14.20 [10.30–24.40] | 11.80 [9.70–15.10] | 0.028* |
| AHI | 5.30 [2.60–9.20] | 4.30 [2.10–8.60] | 0.391 |
| Nocturnal SOREMP | 14 (40.0) | 20 (24.1) | 0.081 |
| RWA | 7 (20.0) | 11 (13.3) | 0.352 |
| RWAI (NT1: $n=7$, NT2: $n=11$) | 2.00 [0.50–6.90] | 1.10 [0.80–7.60] | 0.659 |
| PLM | 15 (42.9) | 25 (30.1) | 0.182 |
| PLMI (NT1: $n=15$, NT2: $n=25$) | 3.70 [0.90–15.60] | 3.00 [1.35–6.40] | 0.455 |
| PLMAr | 11 (31.4) | 17 (20.5) | 0.202 |
| PLMArI (NT1: $n=11$, NT2: $n=17$) | 1.20 [0.20–2.40] | 0.30 [0.20–0.65] | 0.073 |

Drawing upon the PSG outcomes, we meticulously scrutinized the respective observations pertaining to NT1 and NT2, subsequently subjecting these data to rigorous statistical scrutiny aimed at identifying any noteworthy disparities. To this end, we harnessed the Mann-Whitney test for the analysis of medians, while employing the chi-square test for categorical variable. Our investigation unveiled conspicuous elevations in the ArI and WASO within the NT1 cohort, signifying statistical significance in these parameters. In contrast, SE registered a noteworthy decrement in the NT1 group, likewise reaching a level of statistical significance

Values are presented as median [interquartile range], n (%)

*NT* Narcolepsy type, *PSG* Polysomnography, *TST* Total sleep time, *SL* Sleep latency, *SE* Sleep efficiency, *WASO* Wake time after sleep onset, *ArI* Arousal index, *AHI* Apnea hypopnea index, *SOREMP* Sleep onset rapid eye movement period, *RWA* Rapid eye movement sleep without atonia, *RWAI* Rapid eye movement sleep without atonia index, *PLM* Periodic leg movement, *PLMI* Periodic leg movement index, *PLMAr* Periodic leg movement associated with arousal, *PLMArI* Periodic leg movement associated with arousal index

Median [interquartile range] tested by Mann-Whitney U test

n (%) tested by chi-square test

*$P<0.05$

compelling evidence of sleep instability in individuals with NT1 (Brink-Kjaer et al. 2021). Notably, our investigation also ascertained that the ArI in PSG was significantly higher in NT1 when compared to NT2, aligning with the findings of previous research (Sasai-Sakuma et al. 2015). Consequently, the incidence of excessive sleepiness and the prevalence of hypnagogic hallucination, sleep paralysis, and DMS were undeniably more pronounced in NT1, when contrasted with NT2. Particularly with regard to DMS, it appears to be an indispensable characteristic of NT1.

In contrast, although SRMBD also emerged as predominant in NT1 during our investigation, the RWAI and PLMI measurements in PSG, which serve as PSG indicators for SRMBD, did not exhibit significant differences between the two types of narcolepsy in this study. The ICSD-3-TR notes complications such as REM sleep behavior disorder (RBD) or Periodic leg movement disorder (PLMD) in patients with NT1 (AASM 2023). While the scoring methodologies diverged from our method, prior research has suggested that comorbid RBD was present in 43% to 61% of NT1 cases, with an average RWA proportion of 14.3 ± 8.3(%) (Mattarozzi et al. 2008). Particularly noteworthy, among NT1 patients below the age of 18, PSG revealed RWA findings in 80% of cases and 82% in MSLT, with an RWAI of 9.2% during nocturnal PSG and 7.0% in MSLT (Bin-Hasan et al. 2018). Moreover, PLM was reported more frequently in elderly male patients with NT1 (Mattarozzi et al. 2008). However, a previous study in Japan reported similar prevalence rates for RWA and PLM as our data, concluding that these rates are lower than those observed in Western patients (Sasai-Sakuma et al. 2015). Furthermore, our investigation did not ascertain any distinct features associated with RWA and PLM, possibly due to the limited number of patients with confirmed RWA and PLM findings in PSG. Consequently, further investigation is required to evaluate these relationships.

The current study disclosed a 29.7% incidence of NT1 among patients with narcolepsy. The prevalence of NT1 among patients with narcolepsy in Korean adolescents was reported at 30% (Shin et al. 2008), and a previous study conducted in Japan has been documented at 34.9% (Sasai-Sakuma et al. 2015), consistent with our results. However, in western countries, the proportion of NT1 was estimated to be approximately 60% (Silber et al. 2002; Akyildiz et al. 2022), which diverges from our findings. Considering that our diagnosis of NT1 primarily relied on the presence of cataplexy, it is crucial to contemplate the possibility of symptom latency, as a previous study

has demonstrated that most patients developed cataplexy within 4 years (Okun et al. 2002). Given that our patients faced a diagnostic delay ranging from 5 to 7 years, the temporal aspect may not exert full efficacy upon our outcomes. Although the findings of this investigation are based on data from one local hospital in Japan, we posit that our results may signify a predominance of NT2 in Japan. To obtain a more comprehensive understanding, it will be necessary to collect data from diverse regions within Japan and compile them similarly to the present report.

## Conclusion

Patients with NT1 demonstrated higher levels of sleep fragmentation which is explained by the high arousal index and the long wake time after sleep onset on PSG in comparison to those with NT2, and experienced greater difficulty of maintaining sleep. The prevalence of NT1 among patients with narcolepsy in Japan may be lower than that of western countries.

### Abbreviations

| | |
|---|---|
| NT1 | Narcolepsy type 1 |
| NT2 | Narcolepsy type 2 |
| PSG | Polysomnography |
| MSLT | Multiple sleep latency test |
| ICSD-3 | International Classification of Sleep Disorders, Third Edition |
| REM | Rapid eye movement |
| SOREMP | Sleep-onset REM-sleep period |
| JESS | Japanese version of the Epworth Sleepiness Scale |
| DMS | Difficult maintaining sleep |
| SRMBD | Sleep-related movement and behavior disorders |
| BMI | Body mass index |
| TST | Total sleep time |
| SL | Sleep latency |
| SE | Sleep efficiency |
| WASO | Wake time after sleep onset |
| ArI | Arousal index |
| AHI | Apnea-hypopnea index |
| RWA | REM sleep without atonia |
| RWAI | RWA index |
| PLMI | Periodic leg movement index |
| PLMArI | Periodic leg movement associated with arousal index |
| MSL | Mean sleep latency |
| F-SOREMP | Frequency of SOREMP |
| ANCOVA | Analysis of co-variance |
| IQR | Interquartile range |
| SD | Standard deviation |

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### Authors' contributions

K.N. and M.W. wrote the main manuscript text. All authors reviewed the manuscript.

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### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy policy constraints but are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The Chutoen General Medical Center Clinical Research Ethics Committee approved this study (approval number: 1203220810). This investigation was announced to the public on the website of our hospital and all patients could choose to participate or refuse to participate in this study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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