Sleep Medicine 94 (2022) 17–25

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

The REM-sleep-related characteristics of narcolepsy: a nation-wide multicenter study in Turkey, the REMCON study

Utku Ogan Akyildiz [a], F. Irsel Tezer [b], Guray Koc [c], Sevda Ismailogullari [d], Aylin Bican Demir [e], Aysin Kisabay Ak [f], Gulin Sunter [g], Kezban Aslan Kara [h], Deniz Tuncel Berktas [i], Aysenur Sahin [j], Filiz Azman [b], Bulent Devrim Akcay [c], Duygu Kurt Gok [d], Hikmet Yilmaz [f], Kadriye Agan [g], Yavuz Bekmezci [j], Sinan Yetkin [c], Murat Aksu [j], Derya Karadeniz [k], Gulcin Benbir Senel [k, *]

[a] Department of Neurology, Adnan Menderes University Medical Faculty, Aydın, Turkey
[b] Department of Neurology, Hacettepe University Medical Faculty, Ankara, Turkey
[c] Department of Neurology, Gulhane Training and Research Hospital, Ankara, Turkey
[d] Department of Neurology, Erciyes University Medical Faculty, Kayseri, Turkey
[e] Department of Neurology, Uludag University Medical Faculty, Bursa, Turkey
[f] Department of Neurology, Celal Bayar University Medical Faculty, Manisa, Turkey
[g] Department of Neurology, Marmara University Medical Faculty, Istanbul, Turkey
[h] Department of Neurology, Çukurova University Medical Faculty, Adana, Turkey
[i] Department of Neurology, Kahramanmaras Sutcu Imam University Medical Faculty, Kahramanmaras, Turkey
[j] Department of Neurology, Acibadem University Atakent Hospital Medical Faculty, Istanbul, Turkey
[k] Department of Neurology, Sleep and Disorders Unit, Istanbul University-Cerrahpasa, Medical Faculty of Cerrahpasa, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 23 December 2021
Received in revised form
22 March 2022
Accepted 27 March 2022
Available online 2 April 2022

Keywords:
Narcolepsy
REM sleep
REM sleep Without atonia
Rapid eye movement index

ABSTRACT

Introduction: Narcolepsy type 1 (NT1) is caused by hypocretin deficiency, the pathophysiology of narcolepsy type 2 (NT2) has not been delineated. Except for the hypocretin deficiency and cataplexy, all clinical and laboratory features used in the diagnosis of NT2 are identical to those used for NT1. The aim of this study was to assess the rapid eye movement (REM) sleep-related characteristics in the patients with narcolepsy; the characteristics of REM sleep in polysomnography (PSG) and multiple sleep latency test (MSLT) recordings, the quantification of REM sleep without atonia (RSWA) and atonia index, and the analysis of rapid eye movements (REMs) during REM sleep.

Materials and methods: This study was planned by the Sleep Medicine Study Group of the Turkish Neurology Society, and conducted in 11 centers in eight cities in Turkey. The analysis of RSWA was analyzed by reviewing all REM sleep periods on nocturnal PSG and MSLT recordings per standard criteria. The total duration of the increased muscle tone during REM sleep in the chin and bilateral leg electromyography (EMG) recordings was calculated as RSWA index. The REMs index was also investigated the relation to the RSWA.

Results: A total of 274 patients were involved; 147 patients (53.6%) were males and 127 patients (46.4%) were females; the mean age was 29.1 ± 12.0 years. The diagnosis of NT1 was made in 166 patients (60.6%), and 108 patients (39.4%) were diagnosed as having NT2. The mean Epworth sleepiness scale score was significantly higher in patients with NT1 than the patients with NT2 ($P = 0.001$). The diagnosis of REM sleep behavior disorder (RBD) was made in 19.3% of the patients with NT1 versus in 2.8% of the patients with NT2 ($P < 0.001$). The percentage of SOREMP in PSG recordings was significantly higher in patients with NT1 (37.1%) than those with NT2 (18.9%, $P = 0.001$). MSLT showed that the mean sleep latency was shorter in patients with NT1 compared to those with NT2 ($P < 0.001$). The total duration of REMs on electrooculography recordings was also significantly higher in patients with RSWA in comparison with the patients without RSWA ($P = 0.002$). Total duration of REMs was significantly and positively correlated with the duration of RSWA on chin-EMG and leg-EMG recordings ($P = 0.001$). ROC analyses showed an RSWA index of ≥2% for the RSWA on chin-EMG with a sensitivity of 86.7% and a

* Corresponding author. Department of Neurology, Sleep and Disorders Unit, Istanbul University-Cerrahpasa, Medical Faculty of Cerrahpasa, Istanbul, 34098, Turkey.
E-mail address: drgulcinbenbir@yahoo.com (G.B. Senel).

https://doi.org/10.1016/j.sleep.2022.03.025

specificity of 71.3% ($P < 0.001$). The REMs index ≥20% was associated with the presence of RSWA with a sensitivity of 70.0% and a specificity of 57.1% ($P = 0.008$).
Conclusions: In this nation-wide study, we identified for the first time that the increase in REMs density during REM sleep may be a major correlate of the RSWA. Significant positive correlations were demonstrated between the total duration of REMs on electrooculography recordings and the mean durations of RSWA in both chin and leg EMG recordings. A REMs index of >20% was demonstrated to have a moderate sensitivity and specificity in the diagnosis of RSWA. As observed in chin RSWA index, REMs index also showed a significantly high association with RBD, in comparison to RSWA per standard criteria.

1. Introduction

Narcolepsy, one of the central diseases of hypersomnolence, is characterized by the pentad of irresistible sleep attacks, cataplexy, sleep paralysis, sleep-related hallucinations, and disrupted nocturnal sleep [1,2]. Narcolepsy type 1 (NT1), formerly named as narcolepsy-cataplexy syndrome, is caused by the hypocretin deficiency, while the pathophysiology of narcolepsy type 2 (NT2) has not been delineated yet. On the other hand, except for the hypocretin deficiency and the presence of cataplexy, all clinical and laboratory features used in the diagnosis of NT2 are identical to those used for NT1 [3]. Clinically, the excessive daytime sleepiness (EDS) is the cardinal symptom for both types of narcolepsy, and REM (rapid eye movement) sleep-related manifestations like sleep paralysis and sleep-related hallucinations may accompany both types. Disrupted nocturnal sleep is another key symptom of narcolepsy; besides the sleep-related symptoms like REM sleep behavior disorder (RBD) or nightmares, and associated conditions like periodic leg movements or sleep apnea, an intrinsic sleep instability characterized by the frequent spontaneous awakenings and increased sleep stage transitions is defined in narcolepsy, probably due to the hypocretinergic deficiency [2].

Currently, REM sleep-related symptoms other than cataplexy are not used either in the diagnosis of narcolepsy, or in the differential diagnosis of NT1 and NT2. In multiple sleep latency test (MSLT), which is used for the definitive diagnosis of both types, the criteria including sleep latency and the number of sleep-onset REM periods (SOREMP) are also the same for both NT1 and NT2. While the role of the MSLT results are overemphasized in the current international criteria, the sensitivity and specificity of the MSLT is low, and the consistency of the results is questionable [4–6] The latest international classification criteria are therefore being criticized and reappraised to comprise other associated features in narcolepsy [4,7].

Among the clinical features and REM sleep-related manifestations of narcolepsy, cataplexy is the only pathognomonic symptom specific to narcolepsy, constituting an important feature among the diagnostic criteria of NT1. Sleep paralysis and hypnagogic/hypnopompic hallucinations (HH), on the other hand, may commonly accompany NT1 or NT2, and supply additional support in the diagnosis of narcolepsy [4]. Disturbed nocturnal sleep constitutes one of the pentad symptoms of narcolepsy, although it has been somehow neglected in the diagnostic criteria, and also in clinical practice. REM sleep without atonia (RSWA) is another prominent feature in narcolepsy, and a neurophysiological hallmark of RBD [8,9]. It reflects the nocturnal motor disturbance in REM sleep, and is suggested to be used as a diagnostic biomarker in pediatric narcolepsy [10]. Narcolepsy is the most common second cause of secondary RBD following α-synucleinopathies [11]. Although RSWA and/or RBD secondary to narcolepsy may putatively be linked to hypocretin deficiency, it may also be observed in NT2, suggesting the role of other disease-related intrinsic factors causing REM sleep instability. According to the latest international diagnostic criteria [3], the presence of RSWA in polysomnographic (PSG) recordings is mandatory in RBD diagnosis. On the other hand, the current scoring rules for RSWA have been poorly defined, and the need for better quantification by using visual, manual, or automated methods are being suggested [12–14].

The aim of this study was to assess the REM sleep-related characteristics in the patients with narcolepsy; the clinical features known to be related to REM sleep, the characteristics of REM sleep in PSG and MSLT recordings, the quantification of RSWA and atonia index, and the analysis of rapid eye movements (REMs) during REM sleep stage.

2. Methods

This study was planned by the Sleep Medicine Study Group of the Turkish Neurology Society. It was conducted in 11 centers in eight cities in Turkey, and data acquisition was collected for 10 months between January and October 2020. All patients being followed up with the diagnosis of narcolepsy during the study period were consecutively included in to this study. The inclusion criteria were set as follows: (i) the clinical evaluation of all patients by a sleep specialist, (ii) at least one night of PSG and MSLT recordings, and (iii) the diagnosis of narcolepsy (either NT1 or NT2) on the basis of current international criteria [3]. Among exclusion criteria were the use of drugs and/or substances which suppresses REM sleep, the use of hypnotic-sedative drugs and/or substances, a history of systemic and/or neurological diseases and the presence of a structural lesion on cranial neuroimaging. The ethical approval of the study was obtained from the Local Ethics Committee of Aydın Adnan Menderes University, Faculty of Medicine (E−53043469-050.04.04−86817).

A preformed questionnaire and database were formed by the principle researchers (U.O.A. and G.B.S.). The demographical and clinical data were noted in detail, and included age, gender, body mass index (BMI), recent change in weight, detailed history of EDS, cataplexy, sleep paralysis and HH, past medical history, and the use of drugs and/or substances. Epworth sleepiness scale (ESS) and Pittsburgh sleep quality index (PSQI) were assessed. All PSG recordings were performed in accordance with American Academy of Sleep Medicine (AASM) recommendations [15]. All patients had one chin electromyography (EMG) of submentalis muscle and right- and left-sided leg EMG recordings of bilateral tibialis anterior muscles, in addition to other recommended technical specifications. MSLT was performed on the basis of criteria defined by Littner et al [16]. All PSG and MSLT recordings were visually reanalyzed by the neurologists specialized in sleep medicine, who are the collaborators of this study.

The scoring of sleep and associated events were also made in accordance with AASM recommendations [15]. The analysis of RSWA

was analyzed by reviewing all REM sleep periods on PSG and MSLT recordings per standard criteria as follows: The presence of RSWA was scored when excessive sustained muscle activity (at least 50% of the duration of an epoch) was observed in the chin EMG and/or excessive transient muscle activity (at least 50% of 3 s mini-epochs in an epoch) was observed in the chin and/or limb EMG. In PSG recordings, we also calculated the total duration of the increased muscle tone during REM sleep separately in the chin and bilateral leg EMG recordings to have an RSWA index per the total duration of REM sleep stage. The RSWA index (the total duration of RSWA divided by the total duration of REM sleep) was separately calculated for the chin and leg EMG recordings. In the presence of an artefact preventing the evaluation of the muscular activity, the area with artefact was omitted. An increase in the activity in bilateral leg EMG recordings meeting the criteria for a leg movement (LM) event, as defined by the AASM rules, was not counted as an increase in the muscular activity to be scored as RSWA. Similarly, an increase in the activity in the chin EMG associated with an arousal (either spontaneous or related to respiratory events or related to movements such as bruxism) was not counted as a part of RSWA. In addition, we analyzed the rapid eye movements (REMs) during REM sleep stage, which are the pathognomonic phasic elements of REM sleep [17]. We calculated the REMs index by dividing the total duration of REMs on electrooculography (EOG) recordings per the total duration of REM sleep stage, and investigated the relationship of an increase in REMs index with the RSWA. The diagnosis of sleep disorders was made on the basis of clinical history of the patients and PSG and/or MSLT recordings, as defined in the International Classification of Sleep Disorders [3]. On this basis, the behaviors documented by PSG during REM sleep and/or based on clinical history of dream enactment, that are presumed to occur during REM sleep, associated with a PSG recording demonstrating RSWA defined by the AASM [15], were used in the diagnosis of RBD.

The statistical analysis of the study was done by using IBM® SPSS® (Statistical Package for the Social Sciences) statistics version 20.0. The distribution of the parametric data was analyzed by using the Kolmogorov–Smirnov test. In comparative analysis, chi-square test was used for the nominal parameters, the Mann–Whitney *U* test or the Kruskal–Wallis test was used for the parametric data without normal distribution, and the Student *t* test was used for the parametric data with normal distribution. The adjustment of multiple comparisons and the fundamental covariates (including age, sex, and BMI) was made by using a binomial logistic regression for the nominal variables, and by using a univariate general linear model for the continuous variables. A receiver operating characteristic curve and the area under the curve (AUC) was used to analyze the sensitivity and specificity of different RSWA and REMs indices. The correlation analysis between RSWA and REMs indices was performed by using linear regression models. Data were given as percentages or mean ± standard deviation. The statistically significant level was set as a *P* value equal to or lower than 0.05. The false discovery rate for the multiple between-group comparisons was corrected by using the Benjamin–Hochberg procedure, with a false discovery rate of $q = 0.05$.

3. Results

3.1. Clinical assessment

A total of 274 patients were involved into our study from 11 centers in Turkey. Of all patients with narcolepsy, 147 patients (53.6%) were males and 127 patients (46.4%) were females. The mean age of the whole group on admission was 29.1 ± 12.0 years, ranging from 4 years to 68 years. The diagnosis of narcolepsy type 1, on the basis of the presence of cataplexy, was made in 166 patients (60.6%), and 108 patients (39.4%) were diagnosed as having narcolepsy type 2. The clinical characteristics of the patients with NT1 and NT2 are given in Table 1. On these bases, the mean body mass index was significantly higher in patients with NT1 in comparison to those with NT2 ($P = 0.004$), with higher weight gain during the disease course.

The mean age at onset for EDS was lower in patients with NT1 than those with NT2 ($P = 0.049$). The mean ages at onset for HH and sleep paralysis, however, were similar. On the other hand, both HH and sleep paralysis were more commonly associated EDS in NT1 patients than those in NT2 patients ($P < 0.001$ and $P = 0.023$, respectively). Moreover, the mean frequencies of both HH and sleep paralysis were higher in patients with NT1 in comparison to those with NT2 ($P = 0.036$ and $P = 0.001$, respectively). The type of hallucinations was mostly of hypnagogic in both NT1 and NT2 groups, being followed by of hypnopompic type and of mixed type ($P = 0.389$). The type of sleep paralysis, on the other hand, showed significant differences between two groups; although hypnagogic type was the most common type of sleep paralysis in both groups, hypnopompic and mixed types were markedly more common in those with NT1 than the patients with NT2 ($P = 0.043$, Table 1).

Epworth sleepiness scale showed that subjective excessive daytime sleepiness was significantly higher in patients with NT1 than the patients with NT2 ($P = 0.002$), while Pittsburgh sleep quality index was similar between two groups. Restless legs syndrome/Willis-Ekbom disease was diagnosed in 28.6% of patients with NT1, and in 27.2% of patients with NT2 ($P = 0.531$). The diagnosis of RBD was made in 19.3% of the patients with NT1 versus in 2.8% of the patients with NT2 ($P < 0.001$).

3.2. Polysomnographic and MSLT data

The polysomnographic data of the patients with NT1 and NT2 are given in Table 2. In this context, we observed that the mean WASO, the mean percentages of wakefulness and N1 sleep were higher, and the percentage of REM sleep was shorter in patients with NT1 than those with NT2. The mean sleep latency was significantly shorter in NT1 patients in comparison with NT2 patients. The mean REM sleep latency was shorter in NT1, while the difference was not significant (see Table 2). On the other side, the percentage of SOREMP in PSG recordings was significantly higher in patients with NT1 (37.1%) than those with NT2 (18.9%, $P = 0.001$). The mean index of periodic leg movements was also higher in those with NT1 than those with NT2 (see Table 2).

Multiple sleep latency test showed that the mean sleep latency was shorter in patients with NT1 (3.0 ± 2.1 min) in comparison to those with NT2 (4.6 ± 2.5), which was statistically significant ($P < 0.001$). The percentage of SOREM episodes was also significantly higher in the patients with NT1 than those with NT2 (72.4% vs. 64.8%, $P = 0.008$). The presence of N2 sleep stage before SOREM (48.4% vs. 50.0%, $P = 0.513$) and the presence of RSWA in MSLT (67.4% vs. 54.7%, $P = 0.058$) was similar between the patients with NT1 and NT2.

3.3. Characteristics of REM sleep muscle atonia

On the basis of current international criteria (AASM), evaluating either chin-EMG or leg-EMG recordings or both, RSWA was present in 80.2% of whole study group, being similar between two groups (80.5% in NT1 vs 79.5% in NT2, $P= 0.490$). RSWA was detected in 73.8% of patients on chin-EMG, in 54.2% of right-sided leg-EMG, and in 50.9% of left-sided leg-EMG recordings. The mean total durations of loss of atonia in chin EMG and bilateral leg EMG channels were highly significantly higher in patients with RSWA than those without RSWA (given in Table 3). The mean total duration of loss of

Table 1
Demographic and clinical features of the patients with NT1 and NT2.

Parameters	Patients with NT1 (n = 166)	Patients with NT2 (n = 108)	*P*-value
Gender (males, %)	51.8	56.5	0.263
Age on admission (years)	28.4 ± 12.1	30.4 ± 11.7	0.184
Body mass index (kg/m^2)	27.4 ± 5.3	24.9 ± 4.2	0.004
Weight gain after diagnosis (%)	52.9	37.1	0.043
Mean weight gain (kg)	8.6 ± 6.0	5.3 ± 3.5	0.012
Age at onset for EDS (years)	19.3 ± 9.6	21.8 ± 10.2	0.049
Presence of triggering factor (%)	32.5	29.5	0.270
Age at onset for cataplexy	20.6 ± 9.3	–	–
Type of cataplexy (%)			
Partial	55.5	–	–
Generalized	26.2	–	–
Both	18.3	–	–
Frequency of cataplexy (%)			
<5/year	9.4	–	–
<5/month	35.6	–	–
≥5/month	21.3	–	–
≥5/week	33.7	–	–
Presence of hypnagogic/hypnopompic hallucinations (%)	65.7	25.4	<0.001
Age at onset for hypnagogic/hypnopompic hallucinations (years)	20.9 ± 8.4	21.4 ± 9.4	0.807
Type of hallucinations (%)			
Hypnagogic	60.5	64.0	0.389
Hypnopompic	20.2	28.0	
Both	19.3	8.0	
Frequency of hypnagogic/hypnopompic hallucinations (%)			
<5/year	7.3	16.0	0.036
<5/month	37.6	48.0	
≥5/month	29.4	36.0	
≥5/week	25.7	0	
Presence of sleep paralysis (%)	63.9	50.0	0.023
Age at onset for sleep paralysis (years)	21.1 ± 7.4	22.0 ± 10.9	0.762
Type of sleep paralysis (%)			
Hypnagogic	49.5	72.0	0.043
Hypnopompic	31.7	24.0	
Both	18.8	4.0	
Frequency of sleep paralysis (%)			
<5/year	17.1	44.4	0.001
<5/month	42.0	40.7	
≥5/month	19.0	9.3	
≥5/week	21.9	5.6	
Epworth sleepiness scale (points)	17.0 ± 4.6	15.0 ± 4.8	0.002
Pittsburgh sleep quality index (points)	8.6 ± 3.4	8.4 ± 3.4	0.954

Table 2
The comparison of the polysomnographic data in patients with NT1 and NT2.

Data	Patients with NT1 (n = 166)	Patients with NT2 (n = 108)	*P*-value
Total sleep time (min)	432.4 ± 66.7	439.7 ± 53.5	0.762
WASO (min)	55.4 ± 38.9	37.8 ± 37.6	0.001
Sleep latency (min)	6.4 ± 7.6	9.3 ± 9.2	0.019
REM sleep latency (min)	69.0 ± 73.9	73.6 ± 58.8	0.066
Wakefulness (%)	12.6 ± 8.3	9.8 ± 6.8	0.073
N1 sleep (%)	10.6 ± 7.2	7.4 ± 4.2	0.002
N2 sleep (%)	44.2 ± 9.9	46.2 ± 9.8	0.224
N3 sleep (%)	18.2 ± 9.0	16.4 ± 7.0	0.249
REM sleep (%)	17.2 ± 7.4	19.4 ± 5.6	0.011
Apnea-hypopnea index (per hour)	4.5 ± 8.6	2.9 ± 4.2	0.087
Mean oxygen saturation (%)	95.6 ± 1.8	95.8 ± 1.5	0.786
Minimum oxygen saturation (%)	89.6 ± 4.9	91.6 ± 4.6	0.002
Index of periodic leg movements (per hour)	8.0 ± 15.8	4.0 ± 13.8	<0.001
Presence of SOREMPs (%)	37.1	18.9	0.001

atonia was significantly longer on chin-EMG recordings in comparison to those on right- and left-sided leg-EMG recordings (269.4 ± 442.4s vs 84.0 ± 149.0 s and 74.7 ± 140.6 s, correspondingly; P= 0.045). The mean duration of loss of atonia on chin-EMG showed a significant positive correlation with the mean duration of loss of atonia on right-sided leg-EMG and left-sided leg-EMG recordings ($P < 0.001$, for both).

The authors have also calculated the total duration of REMs on EOG recordings, which was also significantly higher in patients with RSWA in comparison with the patients without RSWA ($P = 0.002$, see Table 3). It was observed that, the mean total duration of REMs was significantly and positively correlated with the mean duration of loss of atonia on chin-EMG ($P = 0.001$, $r^2 = 0.046$, $F = 11.0$), on right-sided leg-EMG ($P < 0.001$, $r^2 = 0.072$,

Table 3
The characteristics of the REM sleep without atonia.

RSWA features in whole study population	Patients with RSWA (n = 224)	Patients without RSWA (n = 50)	*P*-value
Mean duration of loss of atonia in chin-EMG (s)	319.9 ± 472.5	39.8 ± 82.0	<0.001
Mean duration of loss of atonia in right-sided leg-EMG (s)	97.2 ± 159.8	23.8 ± 51.3	<0.001
Mean duration of loss of atonia in left-sided leg-EMG (s)	84.7 ± 149.4	29.4 ± 77.4	<0.001
Mean total duration of REMs (s)	1041.2 ± 751.2	749.8 ± 763.4	0.002
RSWA features between NT1 and NT2 groups	**Patients with NT1 (n = 166)**	**Patients with NT2 (n = 108)**	***P*-value**
Mean duration of loss of atonia in chin-EMG (s)	285.0 ± 465.7	240.6 ± 396.9	0.396
Mean duration of loss of atonia in right-sided leg-EMG (s)	87.2 ± 152.2	78.0 ± 143.6	0.894
Mean duration of loss of atonia in left-sided leg-EMG (s)	78.5 ± 148.6	67.8 ± 125.2	0.963
Mean total duration of REMs (s)	1031.6 ± 827.4	917.6 ± 606.8	0.807

$F = 17.4$) and left-sided leg-EMG ($P < 0.001$, $r^2 = 0.103$, $F = 25.8$) recordings (see Fig. 1a–c).

The RSWA index was separately calculated for the total duration of loss of atonia on chin-EMG, right- and/or left-sided leg-EMG recordings, and for the total duration of REMs on EOG recordings, by dividing the durations of loss of atonia or REMs by the total duration of REM sleep stage. On this basis, the best results out of ROC analyses were gained for an RSWA index of ≥2% for the loss of atonia on chin-EMG recordings with a sensitivity of 86.7% and a specificity of 71.3% ($P < 0.001$, see Table 4). Different RSWA indices were calculated for the loss of atonia on right- and/or left-sided leg-EMG; however, we failed to calculate a reliable RSWA index for leg-EMG recordings. Although very high sensitivity ratios up to 100% were obtained, it was in return of very low specificity in between 5 and 10%; concluding that a reliable index for the loss of REM atonia in extremities could not be determined with this calculation method. The calculation of an index of REMs (duration of REMs on EOG recordings divided by the total duration of REM sleep) yielded that ≥20% of REMs period during REM sleep stage was associated with the presence of RSWA with a sensitivity of 70.0% and a specificity of 57.1% ($P = 0.008$, see Table 4).

The comparative analysis of RSWA data in regards to the presence of RBD showed that only 16.2% of patients with RSWA per standard criteria had RBD with an odd's ratio of 0.855 (0.756–0.968, $P = 0.070$). On the other side, 20.8% of patients with an RSWA index of ≥2% for the loss of atonia on chin-EMG recordings had RBD [odd's ratio, 0.751 (0.585–0.965), $P = 0.053$), and 18.8% of patients with a REMs index of ≥20% on EOG recordings had RBD [odd's ratio, 0.842 (0.609–1.165), $P = 0.332$].

In regard to narcolepsy types, the frequency of RSWA per standard criteria was similar between patients with NT1 and NT2; as the mean durations of loss of atonia on chin-, right- or left-sided leg-EMG recordings and the mean duration of REMs were also similar (see Table 3). However, while 64.6% of patients with RSWA per standard criteria had NT1 ($P = 0.071$), 71.7% of patients with a chin RSWA index ≥2% ($P = 0.047$), and 68.3% of patients with a REMs index of ≥20% ($P = 0.064$) had NT1.

4. Discussion

4.1. Clinical assessment

The majority of our study population had NT1 (60.6% vs 39.4%). This data was compatible with the prevalence of NT1 versus NT2 in general population [18,19]. Both NT1 and NT2 generally manifest between the second and third decades of life, though we observed that the patients with NT1 had a younger onset of EDS in our study. This may be speculated to be related to presence and/or severity of the CSF hypocretin deficiency in NT1 [20]. The association of the HH and sleep paralysis was more commonly encountered among our patients with NT1 than those with NT2. Less frequent occurrence of these symptoms—constituting the classical tetrad of NT1—among the patients with NT2 was previously reported [21,22]. Here we also observed that both sleep-related hallucinations and sleep paralysis were mostly of hypnagogic in type, while the patients with NT1 had significantly more common hypnopompic sleep paralysis. Because hypocretin is heavily involved in the regulation of arousal systems in addition to REM sleep modulation, the instability in sleep and behavioral state may be more pronounced in NT1 associated with hypocretin deficiency.

BMI was higher in patients with NT1 in comparison to those with NT2, with higher weight gain during the disease course. In regard to the various hypothalamic functions of the hypocretin, including energy homeostasis and neuroendocrine functions, a higher prevalence of obesity, metabolic syndrome, and endocrine disturbances was reported in the patients with NT1 [23,24]. A higher BMI in NT1 was similarly reported in a recent study in comparison to both NT2 and idiopathic hypersomnia [17,21], though insignificant results have also been reported [25]. The earlier onset of the disease may explain this difference, as the obesity was reported to be more commonly associated with pediatric-onset narcolepsy [26]. The pathophysiologic link between narcolepsy and obesity was explained by a broad hypothalamic involvement in these patients causing a disturbance in the energy metabolism.

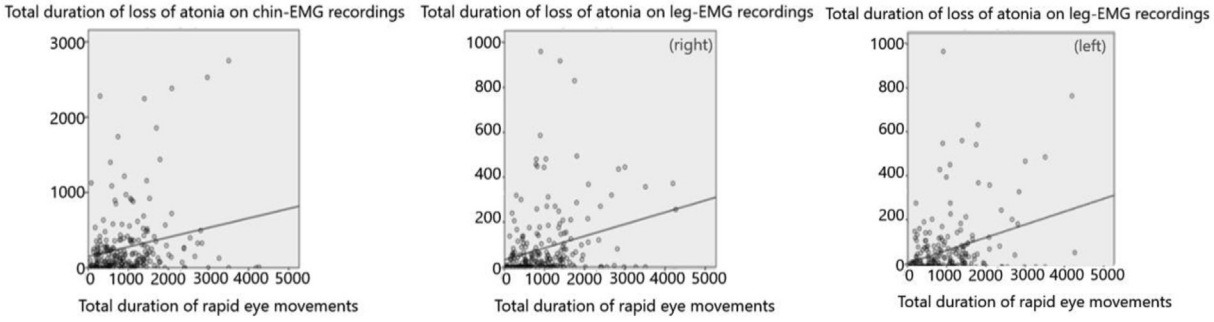

Fig. 1. (a-c) The correlation analysis between REMs and RSWA in chin and leg EMG recordings.

Table 4
The area under curve analysis of RSWA indices for chin EMG, leg EMG, and REMs.

RSWA indices	Sensitivity (%)	Specificity (%)	AUC (S.E.)	95% CI (lower-upper)	*P*-value
Chin index ≥2%	86.7	71.3	0.789 (0.037)	0.717–0.861	<0.001
Chin index ≥3%	88.9	60.9	0.749 (0.038)	0.676–0.823	<0.001
Chin index ≥4%	93.3	51.3	0.725 (0.038)	0.651–0.798	<0.001
Chin index ≥5%	97.8	42.9	0.706 (0.037)	0.633–0.779	<0.001
Leg index ≥2%	93.6	44.3	0.690 (0.036)	0.618–0.761	0.002
Leg index ≥3%	95.7	32.2	0.640 (0.038)	0.565–0.714	0.001
Leg index ≥4%	97.9	23.5	0.607 (0.039)	0.531–0.683	0.008
Leg index ≥5%	100	13.9	0.570 (0.039)	0.492–0.647	0.084
REMs duration ≥15%	52.5	67.3	0.599 (0.051)	0.499–0.699	0.053
REMs duration ≥18%	62.5	61.5	0.620 (0.050)	0.523–0.718	0.019
REMs duration ≥20%	70.0	57.1	0.635 (0.048)	0.541–0.730	0.008
REMs duration ≥22%	72.5	53.2	0.629 (0.048)	0.534–0.723	0.012
REMs duration ≥25%	82.5	44.9	0.637 (0.046)	0.547–0.727	0.008

The subjective daytime sleepiness as measured by ESS was significantly higher in our patients with NT1 than those with NT2, which was also shown in few recent studies [21,27]. The subjective night-time sleep quality, however, was similar between two groups.

The presence of RLS/WED was found to be very high in both types of narcolepsy (28.6% in NT1, and 27.2% in NT2) in this study cohort. RLS/WED was reported to be more prevalent in NT1 being about 15% in contrast to 3% in healthy controls [28]. It was suggested that, different than primary RLS/WED in which brain iron and ferritin levels play an important role in the pathophysiology, RLS/WED associated with NT1 was linked to the alterations in the dopaminergic pathways in narcolepsy [28,29]. Although RLS/WED was more commonly described to be associated with NT1, a higher prevalence in the patients with NT2 than in general population was also reported [30], as supported by our results.

Our data showed that the presence of RBD was especially higher in patients with NT1 (19.3%) in comparison to those with NT2 (2.8%). REM sleep behavior disorder has been reported frequently among the symptoms of narcolepsy, even at first observations [8]. Because the patients with narcolepsy and RBD were reported to be more likely to have cataplexy [8,31], it was suggested that RBD results from intrinsic motor control disturbances in REM sleep resulting from the dysfunction in hypocretin/dopaminergic system, and reflecting the nocturnal phase of sleep-wake instability in patients with narcolepsy [9,13,32]. Nevertheless, 70–90% of patients with NT2 may also have RBD, which may be interpreted as a sign of progression to NT1 [33,34]. Although hypocretin deficiency could not be demonstrated in CSF examinations, postmortem studies have demonstrated partial loss in hypocretinergic neurons in NT2 [35], while a reduced volume in the brainstem raphe volume was also reported in patients with narcolepsy and RBD [36]. It seems that not only the dysfunction in hypocretinergic system, but also the abnormalities in the critical downstream mediators of hypocretin, such as dopaminergic pathways, play a role in the pathophysiology of motor dyscontrol in narcolepsy, leading to RBD.

4.2. Polysomnographic data

While the subjective assessment of night-time sleep quality failed to show a significant difference between two groups, the mean WASO, mean percentages of wakefulness and superficial NREM sleep were significantly higher, and the percentage of REM sleep was significantly shorter in patients with NT1 than those with NT2. Lower sleep efficiency with higher WASO and arousal index were previously demonstrated in patients with NT1 in comparison to those with NT2 [25,37], though contradictory results showing similar macro-architectural sleep in both types are also present [21,38]. These differences among studies may be attributed to the possible misclassification of the patients due to the lack of CSF hypocretin measurements, or the lack of standardized diagnosis of cataplexy or cataplexy-like episodes. Nevertheless, it may also be related to the heterogeneous traits of narcolepsy in general, rather than to type 1 or type 2 specifically.

We observed that the mean sleep latency in nocturnal PSG was significantly shorter in NT1 in comparison to NT2. On the other side, the mean REM sleep latency was shorter in NT1, but not significantly. In the literature, a shorter sleep latency and REM sleep latency in NT1 were reported in nocturnal PSG [21,25,39,40]. It was suggested that short REM sleep latency lower than 15 min during nocturnal PSG was highly specific though not sensitive for patients with narcolepsy associated with hypocretin deficiency [41]. In a recently published paper by Um et al. [42], significant differences were also demonstrated between the patients with NT1 and NT2, characterized by a decreased sleep and REM sleep latency in the patients with NT1 in comparison to those with NT2. Also, the frequency of the SOREMP on nocturnal PSG was reported to be more prevalent in the patients with NT1 than those with NT2. In accordance with this finding, the presence of SOREMP in PSG recordings was significantly more common in patients with NT1 in our study, as well. Changes in REM sleep oscillations driven by hypocretin deficiency may explain an intrinsically earlier-timed REM sleep period in nocturnal PSG secondary to an increased REM sleep pressure, and/or altered interactions between REM-on and REM-off mechanisms.

The mean index of periodic leg movements in sleep was significantly higher in narcolepsy type 1. Although similar results have been reported [30,43–45], contradictory findings were also noted in the literature [21,25]. Higher index of periodic leg movements in sleep has been shown to be associated with a higher arousal index in patients with narcolepsy [45], though it was not the case in our study (data not given). The possible effects of the periodic leg movements in sleep on the perceived sleep quality or daytime sleepiness in narcolepsy wait to be delineated.

4.3. MSLT features

Similar to PSG results, we observed that the mean sleep latency was shorter in MSLT in patients with NT1, and the percentage of SOREMP was also higher. In the literature, a shorter sleep latency and REM sleep latency were reported in MSLT of the patients with NT1 in comparison to the patients with NT2 [39,40]. Although the MSLT features are highly dependable in NT1, its sensitivity and specificity are questionable in NT2 [46–48]. Also, a mean sleep latency <8 min and >2 SOREMP in MSLT could be detected in patients with obstructive sleep apnea syndrome or behaviorally-

induced insufficient sleep syndrome [5,39,49]. The evaluation of the pre-MSLT period by using long-term sleep logs and/or actigraphic recordings was suggested to rule out the false positive results. It was also put forward that novel biomarkers electrophysiologically or biologically are needed for the discrimination of different subtypes of central disorders of hypersomnolence.

Additional features have been defined for the MSLT to support diagnostic significance, such as the presence of SOREMP on nocturnal PSG, SOREMP in MSLT before N2 sleep stage, or the presence of SOREMP from wakefulness or N1 sleep stage on fourth (afternoon) nap in MSLT [6,40,50–52]. Occurrence of at least three SOREMP in MSLT with five naps and one SOREMP in nocturnal PSG were recently reported to have a very high specificity and positive predictive value, in expense of sensitivity [39]. Another suggestion was to include the REM sleep latency, duration, and sleep stage sequences into the MSLT criteria to increase its specificity in narcolepsy [51]. However, these features have mainly been defined in the differentiation of narcolepsy from other disorders of central hypersomnolence, but reported to be nonreliable for the differentiation of NT1 and NT2—probably because of the use of similar electrophysiological diagnostic criteria, as stated by these authors. In this context, we found that the presence of N2 sleep stage before SOREMP in MSLT and the presence of RSWA in MSLT was similar between NT1 and NT2.

4.4. Characteristics of REM sleep muscle atonia

We observed that REM sleep without atonia, as per standard criteria, was present in 80.2% of the whole study group, being similar between two groups. Although lower percentages have been reported since the first identification of RSWA and RBD in narcoleptics [31,53], the recent studies have reported that up to 90% of patients with narcolepsy had RSWA in at least one epoch during the nocturnal PSG [10,54]. The patients with narcolepsy were reported to have a higher percentage of RSWA, especially of phasic type, in comparison to the patients with idiopathic RBD [9]. On the other side, several studies have recently focused on the RSWA index, which was reported to be much higher in the patients with narcolepsy in comparison to other types of disorders of hypersomnolence [8,9,14]. In one recent study [55], REM sleep latency and the REM sleep atonia index were used in combination, which yielded a better identification of the pediatric patients with NT1.

Different methods have been suggested for the determination of RSWA by using a variety of formulas and calculations [12]. A recent study showed that RSWA index (>3%) and tonic RSWA index (>2.2%) were significantly higher in NT1 than in NT2, suggesting these parameters to be used as sensitive and specific markers in distinguishing NT1 from NT2 [14]. In this nation-wide study, an RSWA index of >2% for the loss of atonia on chin-EMG recordings was demonstrated to have a high sensitivity (86.7%) and specificity (71.3%) in the diagnosis of RSWA, while RSWA index for leg-EMG recordings were not reliable. Chin RSWA index showed a significantly high association with RBD in comparison to RSWA per standard criteria. In regard to narcolepsy types, although the frequency of RSWA per standard criteria was similar between two groups, chin RSWA index >2% was significantly more frequently encountered in the patients with NT1 than those with NT2.

Although the motor activity and the behaviors during REM sleep were investigated in detail in many studies [9,31,56], the analysis of REMs, which give the name of the sleep stage, have been neglected in the literature. Actually, an increase in the density of REMs in patients with narcolepsy have been reported in the late 20th century in the literature [9,57,58]. It was also reported that the patients with NT1 demonstrated less eye movements during wake and NREM sleep, and more eye movements during REM sleep in comparison to patients with NT2 and controls [17]. The authors have concluded that the patients with NT1 have an altered distribution of eye movements throughout the sleep stages, probably due to direct or indirect role of the hypocretinergic system in the control of eye movements. Here, we observed a significant and positive correlation between the duration of REMs and the mean durations of RSWA in chin and leg EMG activity. Both REMs and twitches during REM are phasic physiological events of REM sleep, and similarly mediated by the glycinergic and GABAergic inhibitory mechanisms controlling REM atonia and the glutamate-driven excitation of motoneurons [59,60]. An increase in the REMs may therefore be a marker of the dysfunction of the inhibitory-excitatory circuits, which generate the physiological twitches, considering the increase in the twitching activity defines the RSWA and contributes to the pathophysiology of RBD.

On the basis of our results, we may conclude that NT1 and NT2 share many similar characteristics in terms of clinical, PSG and MSLT data, although some differences in terms of frequency and severity exist in between. From a multifactorial approach, the genetic predisposition, environmental factors and the immune system-related dysfunction are the common etiologic factors in NT1 and NT2 [61]. However, the prominent differences in the clinical and laboratory data between NT1 and NT2 need to be explained. It is possible that different phenotypes of the same disease, narcolepsy, may result from the differences in the severity of the hypocretinergic deficiency, or the involvement of the hypocretin-related pathways leading to sleep abnormalities without lowering the hypocretin concentrations in CSF [62]. The use of an intermediate level of hypocretin (between 110 and 200 pg/mL) was also proposed to better aid the diagnosis of the patients with narcolepsy. With the accumulation of data, the current diagnostic criteria for the narcolepsy, and the differentiation of subtypes are being heavily discussed and new formulas are being suggested [4,6,63]. Instead of types 1 and 2, primary (idiopathic) narcolepsy, familial narcolepsy, secondary (symptomatic) narcolepsy, and narcolepsy plus (hereditary forms with additional neurological symptoms) forms were suggested to better classify the clinical entities. It seems that the similarities between NT1 and NT2 shows that they share the same genotype and endotype of the disease, while differences will define the phenotypes of narcolepsy.

There are some strengths and limitations of our study. Our study was a nation-wide study of eight different centers of the country, giving the opportunity to include large numbers of patients with some degree of representation. On the other side, the diagnosis of the patients and the evaluations of the PSG and MSLT recordings were performed by different sleep experts. Also, the delay of the PSG/MSLT after the onset of narcolepsy may recall bias, especially for the sleep paralysis and/or HH. Although a large number of patients with NT1 and NT2 were included, the patients with the other types of central hypersomnolence or healthy individuals were not analyzed in this study. It would be beneficial and interesting to see that how these parameters differ between the patients with narcolepsy and the patients with idiopathic hypersomnia, or healthy subjects. The lack of hypocretin measurements in CSF is an important limitation of this study. The CSF hypocretin levels may have changed the classification of some patients, and some proportion of the patients diagnosed as having NT2 would actually had the diagnosis of NT1. Also, the patients with NT1 might have demonstrated some differences regarding the hypocretin status. Furthermore, the correlation analysis of hypocretin levels with the other parameters of the study would be available, especially with the RSWA data. Human leukocyte antigen (HLA) typing was available only in three centers and investigated in 37 patients of the whole study group, for which it was not included among the

statistical analysis. Nevertheless, our study presents a relatively large and comprehensive state-of-the-art features of narcolepsy from Turkey.

5. Conclusion

Here, we identified for the first time that the increase in REMs density during REM sleep may be one of the major correlates of the RSWA, as REMs are the phasic elements of the REM sleep. Significant positive correlations were demonstrated between the total duration of REMs on EOG recordings and the mean durations of loss of atonia in both chin and leg EMG recordings. Also, the total duration of REMs was significantly higher in patients with RSWA in comparison to those without. A REMs index of >20% was demonstrated to have a moderate sensitivity (70.0%) and specificity (57.1%) in the diagnosis of RSWA. As observed in chin RSWA index, REMs index also showed a significantly high association with RBD, in comparison to RSWA per standard criteria.

Conflict of interest

None declared.

The ICMJE Uniform Disclosffigure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2022.03.025.

References

[1] Dauvilliers Y, Billiard M, Montplaisir J. Clinical aspects and pathophysiology of narcolepsy. Clin Neurophysiol 2003;114:2000–17.
[2] Maski K, Mignot E, Plazzi G, et al. Disrupted nighttime sleep and sleep instability in narcolepsy. J Clin Sleep Med 2022;18(1):289–304.
[3] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[4] Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. Sleep Med Rev 2020;52:101306.
[5] Mignot E, Lin L, Finn L, et al. Correlates of sleep-onset REM periods during the multiple sleep latency test in community adults. Brain 2006;129(Pt 6): 1609–23.
[6] Goldbart A, Peppard P, Finn L, et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin sleep cohort. Sleep 2014;37(6):1043–51.
[7] Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol 2019;15(9): 519–39.
[8] Antelmi E, Pizza F, Franceschini C, et al. REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature? Sleep Med Rev 2020;50: 101254.
[9] Dauvilliers Y, Rompre S, Gagnon JF, et al. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. Sleep 2007;30:844–9.
[10] Bin-Hasan S, Videnovic A, Maski K. Nocturnal REM sleep without atonia is a diagnostic biomarker of pediatric narcolepsy. J Clin Sleep Med 2018;14(2): 245–52.
[11] Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. Nat Rev Dis Primers 2018;4(1):19.
[12] Ferri R, Rundo F, Manconi M, et al. Improved computation of the atonia index in normal controls and patients with REM sleep behavior disorder. Sleep Med 2010;11(9):947–9.
[13] Ferri R, Manconi M, Plazzi G, et al. A quantitative statistical analysis of the submentalis muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. J Sleep Res 2008;17(1): 89–100.
[14] Yon MI, Azman F, Yon ME, et al. Nocturnal rapid eye movement sleep without atonia can Be a diagnostic parameter in differentiating narcolepsy type 1 from type 2. J Clin Neurophysiol 2021;38(3):237–41.
[15] Berry RB, Quan SF, Abreu AR, et al., for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Darien, IL: American Academy of Sleep Medicine; 2020. Version 2.6.
[16] Littner MR, Kushida C, Wise M, et al. Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28(1):113–21.
[17] Christensen JAE, Kempfner L, Leonthin HL, et al. Novel method for evaluation of eye movements in patients with narcolepsy. Sleep Med 2017;33:171–80.
[18] Malter M, Neuneier J, Triller A, et al. Narkolepsie im Erwachsenenalter: Definition, Ätiologie und Behandlung [Narcolepsy in adults: Definition, etiology and treatment]. Fortschr Neurol Psychiatr 2021;89(3):103–13.
[19] Silber MH, Krahn LE, Olson EJ, et al. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002;25(2): 197–202.
[20] Schinkelshoek MS, Lammers GJ, Fronczek R. The development of hypocretin deficiency in narcolepsy type 1 can be swift and closely linked to symptom onset: clues from a singular case. Sleep 2019;42(4):zsz009.
[21] Cairns A, Bogan R. Comparison of the macro and microstructure of sleep in a sample of sleep clinic hypersomnia cases. Neurobiol Sleep Circadian Rhythms 2019;6:62–9.
[22] Khan Z, Trotti LM. Central disorders of hypersomnolence: focus on the narcolepsies and idiopathic hypersomnia. Chest 2015;148:262–73.
[23] Honda Y. Clinical features of narcolepsy: Japanese experience. In: Honda Y, Juji T, editors. HLA in narcolepsy; 1988. p. 24–57.
[24] Ponziani V, Gennari M, Pizza F, et al. Growing up with type 1 narcolepsy: its anthropometric and endocrine features. J Clin Sleep Med 2016;12(12): 1649–57.
[25] Brink-Kjaer A, Christensen JAE, Cesari M, et al. Cortical arousal frequency is increased in narcolepsy type 1. Sleep 2021;44(5):zsaa255.
[26] Zhang M, Inocente CO, Villanueva C, et al. Narcolepsy with cataplexy: Does age at diagnosis change the clinical picture? CNS Neurosci Ther 2020;26(10): 1092–102.
[27] Al Shareef SM, AlAnbay E, AlKhathlan MA, et al. HLA-DQB1*06:02 allele frequency and clinic-polysomnographic features in Saudi Arabian patients with narcolepsy. Sleep Breath 2019;23(1):303–9.
[28] Plazzi G, Ferri R, Antelmi E, et al. Restless legs syndrome is frequent in narcolepsy with cataplexy patients. Sleep 2010;33(5):689–94.
[29] Barateau L, Chenini S, Lotierzo M, et al. CSF and serum ferritin levels in narcolepsy type 1 comorbid with restless legs syndrome. Ann Clin Transl Neurol 2020;7(6):924–31. https://doi.org/10.1002/acn3.510.
[30] Nevsimalova S, Pisko J, Buskova J, et al. Narcolepsy: clinical differences and association with other sleep disorders in different age groups. J Neurol 2013;260(3):767–75.
[31] Nightingale S, Orgill JC, Ebrahim IO, et al. The association between narcolepsy and REM behavior disorder (RBD). Sleep Med 2005;6:253–8.
[32] Antelmi E, Pizza F, Vandi S, et al. The spectrum of REM sleep-related episodes in children with type 1 narcolepsy. Brain 2017;140:1669–79.
[33] Bonakis A, Howard RS, Williams A. Narcolepsy presenting as REM sleep behaviour disorder. Clin Neurol Neurosurg 2008;110:518–20.
[34] Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev 2005;9:269–310.
[35] Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. Sleep 2009;32:993–8.
[36] Unger MM, Möller JC, Ohletz T, et al. Transcranial midbrain sonography in narcoleptic subjects with and without concomitant REM sleep behaviour disorder. J Neurol 2009;256:874–7.
[37] Pizza F, Vandi S, Iloti M, et al. Nocturnal sleep dynamics identify narcolepsy type 1. Sleep 2015;38(8):1277–84.
[38] Jiménez-Correa U, Haro R, Obdulia González R, et al. Correlations between subjective and objective features of nocturnal sleep and excessive diurnal sleepiness in patients with narcolepsy. Arq Neuropsiquiatr 2009;67(4): 995–1000.
[39] Dietmann A, Gallino C, Wenz E, et al. Multiple sleep latency test and polysomnography in patients with central disorders of hypersomnolence. Sleep Med 2021;79:6–10.
[40] Drakatos P, Suri A, Higgins SE, et al. Sleep stage sequence analysis of sleep onset REM periods in the hypersomnias. J Neurol Neurosurg Psychiatry 2013;84:223–7.
[41] Andlauer O, Moore H, Jouhier L, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. JAMA Neurol 2013;70(7):891–902.
[42] Um YH, Oh J, Kim SM, et al. Differential characteristics of repeated polysomnography and multiple sleep latency test parameters in narcolepsy type 1 and type 2 patients: a longitudinal retrospective study. Sleep Breath 2021. https://doi.org/10.1007/s11325-021-02525-7.
[43] Pizza F, Tartarotti S, Poryazova R, et al. Sleep-disordered breathing and periodic limb movements in narcolepsy with cataplexy: a systematic analysis of 35 consecutive patients. Eur Neurol 2013;70:22–6.
[44] Dauvilliers Y, Pennestri M-H, Petit D, et al. Periodic leg movements during sleep and wakefulness in narcolepsy. J Sleep Res 2007;16:333–9.
[45] Bahammam A. Periodic leg movements in narcolepsy patients: impact on sleep architecture. Acta Neurol Scand 2007;115(5):351–5.
[46] Cairns A, Trotti LM, Bogan R. Demographic and nap-related variance of the MSLT: results from 2,498 suspected hypersomnia patients: clinical MSLT variance. Sleep Med 2019;55:115–23.
[47] Lopez R, Doukkali A, Barateau L, et al. Test-Retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. Sleep 2017;40(12).
[48] Ruoff C, Pizza F, Trotti LM, et al. The MSLT is repeatable in narcolepsy type 1 but not narcolepsy type 2: a retrospective patient study. J Clin Sleep Med 2018;14(1):65–74.
[49] Mayer G, Lammers GJ. The MSLT: more objections than benefits as a diagnostic gold standard? Sleep 2014;37(6):1027–8.

[50] Kawai R, Watanabe A, Fujita S, et al. Utility of the sleep stage sequence preceding sleep onset REM periods for the diagnosis of narcolepsy: a study in a Japanese cohort. Sleep Med 2020;68:9–17.
[51] Murer T, Imbach LL, Hackius M, et al. Optimizing MSLT specificity in narcolepsy with cataplexy. Sleep 2017;40(12).
[52] Pizza F, Vandi S, Detto S, et al. Different sleep onset criteria at the multiple sleep latency test (MSLT): an additional marker to differentiate central nervous system (CNS) hypersomnias. J Sleep Res 2011;20(1 Pt 2): 250–6.
[53] Schenck CH, Mahowald MW. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. Ann Neurol 1992;32:3–10.
[54] Frauscher B, Ehrmann L, Mitterling T, et al. Delayed diagnosis, range of severity, and multiple sleep comorbidities: a clinical and polysomnographic analysis of 100 patients of the innsbruck narcolepsy cohort. J Clin Sleep Med 2013;9(8):805–12.
[55] Silvani A, Vandi S, Pizza F, et al. Combining information on nocturnal rapid eye movement sleep latency and atonia to facilitate diagnosis of pediatric narcolepsy type 1. Sleep 2021;44(3):zsaa203.
[56] Antelmi E, Pizza F, Donadio V, et al. Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients. Ann Clin Transl Neurol 2019;6(9): 1872–6.
[57] Geisler P, Meier-Ewert K, Matsubayshi K. Rapid eye movements, muscle twitches and sawtooth waves in the sleep of narcoleptic patients and controls. Electroencephalogr Clin Neurophysiol 1987;67:499–507.
[58] Vankova J, Nevsimalova S, Sonka K, et al. Increased REM density in narcolepsy-cataplexy and the polysymptomatic form of idiopathic hypersomnia. Sleep 2001;24:707–11.
[59] Brooks PL, Peever J. A temporally controlled inhibitory drive coordinates twitch movements during REM sleep. Curr Biol 2016;26(9):1177–82.
[60] Aserinsky E. Rapid eye movement density and pattern in the sleep of normal young adults. Psychophysiology 1971;8:361–75.
[61] Latorre D, Kallweit U, Armentari E, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature 2018;562:63–8.
[62] Andlauer O, Moore H, Hong SC, et al. Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. Sleep 2012;35(9):1247–55.
[63] Fronczek R, Arnulf I, Baumann CR, et al. To split or to lump? Classifying the central disorders of hypersomnolence. Sleep 2020;43(8):zsaa044.