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Original Article

First rapid eye movement sleep periods and sleep-onset rapid eye movement periods in sleep-stage sequencing of hypersomnias

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ABSTRACT

Objectives: Discrimination between narcolepsy, idiopathic hypersomnia, and behavior-induced inadequate sleep syndrome (BIISS) is based on clinical features and on specific nocturnal polysomnography (NPSG) and multiple sleep latency test (MSLT) results. However, previous studies have cast doubt on the specificity and sensitivity of these diagnostic tools.
Methods: Eleven variables of the NPSG were analyzed in 101 patients who were retrospectively diagnosed with narcolepsy with cataplexy (N + C) ($n = 24$), narcolepsy without cataplexy (N–C) ($n = 38$), idiopathic hypersomnia with long sleep period (IHL) ($n = 21$), and BIISS ($n = 18$).
Results: Fifteen out of 24 N + C and 8 out of 38 N–C entered the first rapid eye movement (REM) sleep period (FREMP) from sleep stage 1 (N1) or wake (W), though this sleep-stage sequence did not arise in the other patient groups. FREMP stage sequence was a function of REM sleep latency (REML) for both N + C and N–C groups. FREMP stage sequence was not associated with mean sleep latency (MSL) in N + C but was associated in N–C, which implies heterogeneity within the N–C group. REML also was a useful discriminator. Depending on the cutoff period, REML had a sensitivity and specificity of up to 85.5% and 97.4%, respectively.
Conclusions: The FREMP stage sequence may be a useful tool in the diagnosis of narcolepsy, particularly in conjunction with sleep-stage sequence analysis of sleep-onset REM periods (SOREMPs) in the MSLT; it also may provide a helpful intermediate phenotype in the clarification of heterogeneity in the N–C diagnostic group. However, larger prospective studies are necessary to confirm these findings.

1. Introduction

The nocturnal polysomnography (NPSG) and multiple sleep latency test (MSLT) remain important diagnostic tools for the diagnosis of narcolepsy. The International Classification of Sleep Disorders, 2nd edition (ICSD2) [1], states that the NPSG and MSLT are mandatory for the diagnosis of narcolepsy without cataplexy (N–C) in the absence of measurement of cerebrospinal fluid (CSF) hypocretin-1 these tests also are essential for the diagnosis of idiopathic hypersomnia (IH) and should be performed whenever possible for the diagnosis of narcolepsy with cataplexy (N + C).

However, the MSLT is not a gold standard for diagnosis and has considerable issues regarding sensitivity and specificity. In a retrospective analysis of 2472 MSLTs [2], 6% of patients with sleep-disordered breathing and 4% of patients with other sleep disorders met the ICSD2 MSLT definition for narcolepsy. Moreover, some patients only met the diagnostic criteria for narcolepsy after multiple MSLTs, implying the presence of false-negative results. In another study, NPSGs and MSLTs were performed on 556 healthy subjects [3]. A mean sleep latency (MSL) of 8 min or less with two or more sleep-onset rapid eye movement (REM) periods (SOREMPs) was demonstrated in 5.9% of men and 1.5% of women, all of whom did not have cataplexy. This finding implies that either narcolepsy is grossly underdiagnosed or that the MSLT has a high false-positive rate when using the ICSD2 criteria.

More recently an analysis of sleep-stage sequence in naps with SOREMPs demonstrated that 15% of patients with behavior-induced inadequate sleep syndrome (BIISS) met ICSD2 MSLT criteria for narcolepsy [4]. However, this study also demonstrated the potential utility of SOREMP sleep-stage sequence analysis. A significant difference between patients with N + C and BIISS was seen in the MSLT, with REM sleep following sleep stage 1 (N1) in 71% of SOREMPs in patients with N + C. In contrast, only 15% of SOREMPs

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were seen in those patients with BIISS, in which REM sleep mostly was entered from sleep stage 2 (N2) [4]. Subsequent analysis has confirmed this finding and has demonstrated that SOREMPs arising from N1 or wake (W) appear to be more specific to narcolepsy rather than BIISS, IHL, or periodic limb movement disorder (PLMD) [5].

Regarding issues surrounding specificity and sensitivity of the MSLT for narcolepsy and the high incidence of BIISS compared to narcolepsy, we have examined the NPSG to identify further markers of the sleep study that might help to further discriminate between the various hypersomnias. The apparent utility of sleep-stage sequencing of the SOREMPs in the MSLT [5] has led us to apply this technique to the NPSG, specifically for the FREMP of the NPSG.

2. Methods

We retrospectively ascertained all patients who underwent NPSG followed by MSLT the next morning at Guy's and St. Thomas' Sleep Disorders Centre between August 2008 and March 2012. All patients had been evaluated by an experienced sleep physician prior to their sleep study and were required to complete a sleep diary or 2 weeks of actigraphy prior to the study. Appropriate approval was obtained from the trust. Data from the retrospectively ascertained patients were kept anonymous.

The NPSG montage included frontal (F3 and F4), central (C3 and C4) and occipital (O1 and O2) electrodes with auricular reference electrodes, two electrooculographic channels, two submental electromyographic channels, electrocardiography, electromyographic channel on anterior tibialis bilaterally, pulse oximetry, nasal cannula, and respiratory inductance plethysmography with chest and abdominal belts. Sleep stages were scored using 30-s epochs according to standard criteria by the American Academy of Sleep Medicine [6].

The MSLTs were performed according to standard guidelines using central (C3 and C4) and occipital (O1 and O2) electrodes for the montage with auricular reference electrodes, two electrooculographic channels, two submental electromyographic channels, and electrocardiography [7]. Patients took four or five naps under standard MLST conditions, each lasting 20 min, at 2-h intervals on the following day.

Patients were subsequently reviewed with the results of the NPSG and MSLT and the diagnoses of N + C, N−C, IHL, and BIISS were made in accordance with ICSD2 criteria [1]. Exclusion criteria were diagnostic doubt (e.g., possible influence of comorbidities such as obstructive sleep apnea [OSA], PLMD, or psychiatric disease); incomplete clinical information; less than 6 h of sleep during NPSG; or a failure to stop all medications that affect sleep.

All NPSGs were analyzed and several variables were derived for further examination: (1) sleep efficiency, sleep-onset, REM sleep latency (REML), total REM sleep duration, and proportion of the four sleep stages in total sleep time; (2) the stage of which FREMP on NPSG arose; (3) the REM transition index, calculated as number of transitions from REM sleep to another sleep stage over total REM sleep duration; and (4) the total arousal index composed of respiratory-related arousal index, limb movement arousal index, spontaneous arousal index, and major body movements.

The MSLTs of these patients were analyzed in a previous study [5] regarding the sleep-stage sequence of SOREMPs and its correlation with the MSL. Statistical analysis was performed using the SPSS statistical analysis program (SPSS 17.0). Data are reported as mean ± standard deviation if not otherwise indicated. Following testing for normality, similarity of two means was compared using the Student t test and the χ^2 test in case of normal distribution; otherwise, the Wilcoxon signed rank test was used. Comparisons between N + C, N−C, BISS, and IHL groups were made using one-way analysis of variance with post hoc analysis and the least significant difference (LSD). Receiver operating characteristic analysis was used to assess the diagnostic performance of REML in predicting the diagnosis of narcolepsy. We considered $P < .05$ to be statistically significant.

3. Results

Over a 3.5-year period, a total of 257 consecutive patients were identified for analysis. Twenty-six patients were excluded due to

Table 1
Demographics and comparison of nocturnal polysomnographic variables among the groups.

	N + C	N−C	IHL	BIISS	*P* value
Sex (men:women)	7:17	25:13	5:16	7:11	.004
Age (y)	31 ± 12	34 ± 9	34 ± 12	44 ± 13	.004
BMI (kg)	29 ± 6	27 ± 5	28 ± 8	30 ± 8	n.s.
Sleep efficiency (%)	87 ± 6	89 ± 7	89 ± 7	84 ± 13	<.05[a]
Sleep onset (min)	6 ± 5.8	7.7 ± 7	11 ± 7.3	14 ± 17.5	<.05[b]
REML (min)	29 ± 36	57 ± 34	137 ± 58	103 ± 65	<.05[c]
Total REM duration (min)	79 ± 17	82 ± 26	85 ± 27	77 ± 33	n.s.
N1 (%)	11 ± 6	7 ± 5	5 ± 3	9 ± 12	<.05[d]
N2 (%)	43 ± 8	43 ± 10	46 ± 8	48 ± 7	n.s.
N3 (%)	27 ± 7	30 ± 9	29 ± 8	23 ± 9	<.05[e]
REM (%)	19 ± 5	20 ± 6	20 ± 6	20 ± 7	n.s.
Arousal index* (#/h)	20 ± 8	15 ± 7	15 ± 6	19 ± 12	<.05[f]
REM transition index (#/total REM)	7 ± 4	6 ± 4	5 ± 3	7 ± 7	n.s.
FREMP arise from N1 or W	15/24	8/38	0/21	0/18	<.05[g]

Abbreviations: N + C, narcolepsy with cataplexy; N−C, narcolepsy without cataplexy; IHL, idiopathic hypersomnia with long sleep period; BIISS, behavioral-induced inadequate sleep syndrome; y, years; BMI, body mass index; min, minutes; REML, rapid eye movement sleep latency; REM, rapid eye movement sleep; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; h, hours; REM transition index, transitions (#) to another sleep stage over total REM sleep; FREMP, first REM period; W, wake; n.s., not significant.

* Arousal index includes any cause of arousal (e.g., limb movement, major body movement, respiratory arousal).

[a] $P < .05$ only for N−C vs BIISS ($P = .02$) and for IHL vs BIISS ($P = .04$). Analysis of variance (ANOVA) with post hoc analysis least significant difference (LSD).

[b] $P < .05$ only for N + C vs BIISS ($P = .007$) and for N−C vs BIISS ($P = .021$). ANOVA with post hoc analysis LSD.

[c] $P < .05$ for all combinations, N + C vs N−C ($P = .022$), N + C vs IHL ($P < .0001$), N + C vs BIISS ($P < .0001$), N−C vs IHL ($P < .0001$), N−C vs BIISS ($P = .001$), IHL vs BIISS ($P = .02$). ANOVA with post hoc analysis LSD.

[d] $P < .05$ only for N + C vs N−C ($P = .021$) and for N + C vs IHL ($P = .005$). ANOVA with post hoc analysis LSD.

[e] $P < .05$ only for N−C vs BIISS ($P = .006$) and for IHL vs BIISS ($P = .039$). ANOVA with post hoc analysis LSD.

[f] $P < .05$ only for N + C vs N−C ($P = .018$), N + C vs IHL ($P = .039$), and for N−C vs BIISS ($P = .05$). ANOVA with post hoc analysis LSD.

[g] Results of the χ^2 test.

Table 2
Specific rapid eye movement sleep latency values to predict the diagnosis of narcolepsy vs behavioral-induced inadequate sleep syndrome and idiopathic hypersomnia with long sleep period.

REML (min)	Sensitivity	95% CI	Specificity	95% CI
⩽15.5	35.48	23.7–48.7	97.44	86.5–99.9
⩽25	37.10	25.2–50.3	97.44	86.5–99.9
⩽50	50.00	37.0–63.0	94.87	82.7–99.4
⩽70	74.19	61.5–84.5	82.05	66.5–92.5
⩽72*	85.48	74.2–93.1	79.49	63.5–90.7

Abbreviations: REML, rapid eye movement sleep latency; min, minutes; CI, confidence interval.
Computed with receiver operator characteristic analysis (area under the curve, 0.871).
Standard error: 0.0359 (95% confidence interval, 0.790–0.930).
z statistic, 10.352; $P < .001$.
* Criterion corresponding with highest Youden index [11].

lack of clinical information, six due to technical issues relating to their sleep study, and 124 due to coexisting diagnoses or diagnostic uncertainty; many of those excluded had coexisting PLMD, OSA, or a psychiatric disorder. There were 101 patients that were categorized into firm diagnostic categories of N + C ($n = 24$), N−C ($n = 38$), IHL ($n = 21$), and BIISS ($n = 18$). Four BIISS patients demonstrated one or more SOREMPs, and six patients with BIISS had a MSL over 8 min. One patient with BIISS met both diagnostic criteria for narcolepsy on the MSLT. The descriptive variables of the patients and NPSG parameters for each group are shown in Table 1.

A few significant differences were seen in sleep architecture between the four groups. As expected [8,9] patients with N + C and N−C had a significantly shorter sleep latency and REML than the other groups. A receiver operating characteristic analysis demonstrated that utilizing a REML ⩽72 min had a sensitivity and specificity for narcolepsy of 85.5% and 79.5%, respectively. By using shorter cutoff periods for the REML, the measure alone had a specificity of up to 97.5%, though a lower sensitivity of 37% was observed (Table 2) [10].

Sleep efficiency was similar in all patients with the exception of the BIISS group, in which patients exhibited a marginally significantly poorer efficiency. Further analysis of proportion of sleep stages revealed differences between groups. The N + C group demonstrated a significantly higher proportion of N1 compared to IHL and a marginal difference when compared to N−C. In addition, the N−C and IHL groups demonstrated a higher proportion of sleep stage 3 (N3). No significant difference was found in the REM transition index between groups. However, the arousal index of N + C and BIISS groups was higher compared to patients in the other two groups.

Analysis of FREMPs of the NPSG demonstrated that 62.5% of patients with N + C and 21% of patients with N−C entered the FREMP from N1 or W. In contrast, this phenomenon was not seen in any patients with IHL or BIISS (Table 3). In both narcolepsy groups, there were significant differences in REML between patients with FREMPs arising from N1 or W and those with FREMPs arising from other stages.

In the N + C group, those patients with FREMPs arising from N1 or W had a significantly shorter REML of 3.5 ± 2 min and 0.5 ± 0.7 min, respectively, compared to those with FREMPs from N2 (71.5 ± 21 min; $P < .0001$). Linear regression analysis demonstrated a strong correlation between FREMP sleep stage and REML ($R^2 = 0.877$; $P < .0001$). Similarly, in the N−C group patients with FREMPs arising from N1 or W had a shorter REML than those arising from N2 (27 ± 35 min and 70 ± 30 min, respectively; $P < .001$).

All of the patients in our study proceeded to participate in MSLTs; the analysis of MSLT data and sleep-stage sequencing have been previously reported [5]. Analysis of FREMPs in conjunction with MSLT data demonstrated that N + C patients with SOREMPs from N1 or W also were more likely to have the FREMP arising from N1 or W ($P < .0001$). The same finding also was demonstrated in the N−C group ($P < .0001$; Table 4).

In the N + C group, there was no significant influence of FREMP stage sequence on MSL in the MSLT. However, in the N−C group those patients with the FREMP arising from N1 or W did demonstrate a significantly shorter MSL ($P < .0001$). Furthermore, N−C patients with SOREMPs only from N2 did not exhibit FREMPs from N1 or W.

4. Discussion

Our retrospective study of carefully phenotyped patients has demonstrated that there are significant differences in the sleep-stage sequence of FREMPs in patients with N + C, N−C, IHL, and BIISS. Patients with other sleep comorbidities potentially affecting sleep architecture were excluded in an attempt to isolate the influence of narcolepsy on sleep-stage sequence; exclusion of patients with OSA resulted in an apparent equivalent body mass index in those patients with N + C and in the other groups (Table 1).

Only patients with narcolepsy had FREMPs arising from N1 or W, even when FREMPs occurred late in the NPSG. Furthermore, entering REM from N1 or W was associated with a shorter REML, which implies that these patients have increased REM pressure. Indeed, these findings are similar to a recent study that demonstrated that individuals with narcolepsy and in particular those with cataplexy, exhibited higher numbers of SOREMPs during the day in both the MSLT and in daytime polysomnography. These findings imply that dysregulation of the W and REM transition is a specific feature of narcolepsy, particularly in the context of cataplexy or low hypocretin levels [11]. This hypothesis is further reinforced by studies implicating hypocretin in modulation of the sleep-wake transition [12]. Previous findings also suggest an increased drive for REM in narcolepsy and a weaker drive in IHL [1,8,13], resulting in a shorter REML in narcoleptics; presumably it is this increased REM pressure that underlies the hallmark features of hypnagogic hallucinations and sleep paralysis in narcolepsy. Indeed a REML ⩽72 min had a sensitivity and specificity for narcolepsy of 85.5% and 79.5%, respectively.

In contrast, FREMP sleep-stage sequence appeared to have little association with MSL latency in the MSLT, with the exception that those patients with N−C who exhibited FREMPs that arose from N2

Table 3
Tendency of the groups to have first rapid eye movement sleep period from different sleep stages.

Sleep stage entering FREMP	N + C	N−C	IHL	BIISS
N1	13/24 (54%)	7/38 (19%)	0/21 (0%)	0/18 (0%)
N2	9/24 (37%)	24/38 (63%)	19/21 (90%)	16/18 (88%)
N3	0/24 (0%)	6/38 (16%)	2/21 (10%)	4/18 (22%)
W	2/24 (9%)	1/38 (2%)	0/21 (0%)	0/18 (0%)

Abbreviations: FREMP, first rapid eye movement sleep period; N + C, narcolepsy with cataplexy; N−C, narcolepsy without cataplexy; IHL, idiopathic hypersomnia with long sleep period; BIISS, behavioral induced inadequate sleep syndrome; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; W, wake.

Table 4
Tendency of the narcoleptics to have first rapid eye movement periods arising from stage 1 sleep or wake in conjunction with sleep-onset rapid eye movement periods arising only from stage 1 sleep or wake.

	N + C (n = 24)	N−C (n = 38)
FREMP (N1 or W)	15/24	8/38
FREMP (N1 or W)/ SOREMPs (N1, W)	13/17[a]	5/13[b]
FREMP (N1 or W)/ SOREMPs (not from N1, W)	2/7[a]	3/25[b]

Abbreviations: FREMP, first rapid eye movement sleep period; N + C, narcolepsy with cataplexy; N−C, narcolepsy without cataplexy; N1, stage 1 sleep; W, wake; SOREMPs, sleep-onset rapid eye movement periods.

[a] $P < .0001$; Fisher exact test. Proportion of N + C with FREMP from N1 or W and SOREMP from N1 or W vs N + C with FREMP from N1 or W without SOREMPs from N1 or W.

[b] $P < .0001$; Fisher exact test. Proportion of N−C with FREMP from N1 or W and SOREMP from N1 or W vs N + C with FREMP from N1 or W without SOREMPs from N1.

or N3 had a longer MSL. N−C patients with FREMPs arising from N1 or W had similar MSLs to those patients with N + C. Therefore, there appeared to be a subset of patients with N−C that had a shared phenotypic characteristics to those patients with N + C, while another subset was fundamentally different; this finding implies significant heterogeneity within the N−C population.

Only a few of the features of the NPSG were significantly different between patient groups. Sleep latency was significantly shorter for those with a hypersomnia of central origin, especially for narcoleptics rather than BIISS, which is consistent with previous studies [8,11,13–15]. In our study, the BIISS group only had a marginally significantly lower sleep efficiency compared to N−C group and IHL group, though no significant difference was found between N + C and N−C; this finding is in contrast to previous studies [1,13]. The N + C group demonstrated the highest proportion of N1, but the proportion only was significant when compared to IHL and was marginal when compared to N−C [1,13]. With regard to other non-REM sleep stages, only the N−C group showed a significantly higher percentage of N3 compared to BISS. Similar to previous studies, the percentage of REM sleep was similar in all groups [1,13], as were the REM duration and the REM transition index. These findings suggest that, although narcoleptics have an altered drive to REM, this does not influence REM stability or a need for increased REM sleep.

The diagnosis of narcolepsy remains problematic. This issue is less of a concern for narcolepsy with cataplexy, in which a clinical history of cataplexy rather than cataplexy-like episodes [16] is pathognomonic. In addition, there is a biochemical marker, the deficiency or absence of CSF hypocretin-1, which approximates a gold standard for diagnosis [17,18]. However, at present the diagnosis of N−C primarily is based on the clinical picture of excessive daytime sleepiness with features of short REML, manifesting as sleep paralysis and hypnagogic hallucinations. This diagnosis is backed by the MSLT, a physiologic test of short REML and short sleep latency. Unfortunately, it is apparent that the intermediate phenotype of SOREMPs is prone to false-positive and false-negative results [3,4], and therefore the MSLT is far from a gold standard for diagnosis of this condition. Equally the CSF hypocretin-1 level and HLA haplotype are not helpful in defining the entity of N−C, as the former only is deficient or low in approximately 20% and the latter is positive in approximately 50% to 60% of patients [19–21]. However, these genetic or biochemical markers do suggest that some patients with N−C have a shared pathophysiology with N + C [20], especially the small proportion who are HLA^+ and deficient in CSF hypocretin-1; however, these characteristics also may represent patients who will subsequently go on to develop cataplexy [22,23].

At least based on pathophysiologic assumptions, it therefore appears that N−C is a heterogeneous condition. Some cases may represent unrecognized BIISS [4], and others may represent a condition within the spectrum of idiopathic hypersomnia [24]. Further, other cases may represent N + C but with unrecognized cataplexy or a case of cataplexy that has yet to develop. However, although the current basis of the diagnosis is heavily based on clinical features and a sleep study, it would seem logical to attempt to dissect this heterogeneity by utilizing features of the clinical presentation and the sleep study. Previous work has implied that sleep-stage sequencing of SOREMPs in the MSLT may be helpful [5]. Additionally, our study also implies that sleep-stage sequencing in the NPSG also might have some utility, particularly in that of the first REML period of the night. Indeed analysis of FREMP sleep-stage sequencing in the context of SOREMP sleep-stage sequencing in the MSLT revealed that none of the patients with IHL or BIISS had FREMPs or SOREMPs arising from N1 or W. Conversely by utilizing FREMP or SOREMP sleep sequencing as a hypothetical diagnostic tool (i.e., the presence of a FREMP or SOREMP arising from N1 or W), this technique demonstrated a specificity of 100% for narcolepsy and a sensitivity of 88% for diagnosing N + C and 47% for diagnosing N−C. Of course, it is possible that those patients demonstrating this sequence represented a subgroup of patients with unrecognized or preclinical cataplexy.

Clearly there are major limitations to these figures, as our patient groups were defined according to ICSD2 diagnostic criteria, with two or more SOREMPs on the MSLT. The patient groups were small and retrospectively ascertained, and the data of HLA haplotype and CSF hypocretin-1 levels were notably lacking.

However, these data certainly raised the possibility that FREMP and SOREMP sleep-stage sequencing may have clinical and research utility. They also highlight the necessity of larger-scale prospective studies of carefully phenotyped patients with ample HLA and CSF hypocretin data and patient groups with other sleep pathologies, such as OSA and PLMD. It remains unclear if sleep-stage sequencing has a high concordance with HLA type or CSF hypocretin-1 levels.

However, the identification of a phenotypically pure subset of patients with N−C seems fundamental to understanding the genetic or immunologic basis of the condition, as well as its relationship to other hypersomnias of central origin. We propose that FREMP and SOREMP sleep-stage sequencing may be important intermediate phenotypic markers in an iterative process to more closely define this disease entity.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.03.021.

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