Usefulness of a Nocturnal SOREMP for Diagnosing Narcolepsy with Cataplexy in a Pediatric Population

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Study Objectives: We investigated the diagnostic accuracy of a nocturnal sleep onset rapid eye movement sleep period (nSOREMP) for the identification of narcolepsy with cataplexy (N+C) among children and adolescents referred to the sleep laboratory for an overnight polysomnography (PSG) and multiple sleep latency test (MSLT).
Design: Retrospective chart review of sleep clinic notes and PSG and MSLT reports.
Setting: Boston Children's Hospital sleep laboratory and outpatient clinics.
Patients: All patients 6–18 y old, referred for consecutive PSG and MSLT for the evaluation of central hypersomnias, between January 2005 and January 2014.
Measurements and Results: We analyzed the records of 148 patients and established diagnostic categories using the International Classification of Sleep Disorders, 2nd Edition. Patient diagnoses included narcolepsy with cataplexy (28.4%), narcolepsy without cataplexy (8.1%), other hypersomnia conditions (9.5%), delayed sleep phase syndrome (12.2%), behaviorally induced insufficient sleep syndrome (4.1%), other sleep disorders (obstructive sleep apnea, periodic limb movements of sleep; 6.8%), isolated cataplexy (2%), and various diagnoses (29.1%). There were 54.8% of the N+C patients who had an nSOREMP, but only 2.4% of all other patients had an nSOREMP. The specificity of an nSOREMP for detection of N+C was high at 97.3% (95% confidence interval [CI]: 92.2–99.4%), but the sensitivity was moderate at 54.8% (95% CI: 38.7–70.2%). Overall, the positive predictive value of an nSOREMP for the diagnosis of N+C was 88.5% (95% CI: 69.8–97.4%).
Conclusions: In children, the presence of an nocturnal sleep onset rapid eye movement sleep period is highly suggestive of narcolepsy with cataplexy and provides further evidence of rapid eye movement sleep dysregulation in this condition.
Keywords: cataplexy, children, MSLT, narcolepsy, nocturnal SOREMP, REM latency
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INTRODUCTION

Though most patients develop narcolepsy with cataplexy (N+C) in childhood or adolescence,[1] the diagnosis is frequently missed until adulthood.[2] This delay in diagnosis may be caused by difficulty recognizing core symptoms of N+C. Pediatric patients with narcolepsy commonly present with excessive daytime sleepiness (EDS), but EDS is reported in up to 15% of all school-aged children[3] and lacks diagnostic specificity. Furthermore, children and adolescents may not report symptoms of hypnogogic/hypnopompic hallucinations, cataplexy, and/or sleep paralysis to their parents or guardians, and depending on their age, they may have difficulty understanding these symptoms when queried by a physician. Children may also have atypical presentations of cataplexy, with partial cataplexy, cataplectic facies, and unusual emotional precipitants[4] that may result in diagnostic uncertainty. Given the challenges and limitations of measuring cerebrospinal fluid hypocretin, the overnight polysomnography (PSG) and multiple sleep latency test (MSLT)

remain the essential tests for diagnosing narcolepsy with and without cataplexy.[5,6]

On the MSLT, patients with narcolepsy usually have mean sleep latencies less than 5 min and multiple sleep onset rapid eye movement (REM) sleep periods (SOREMPs).[7] Retrospective surveys have shown that these results from the MSLT are highly sensitive for detecting patients with confirmed N+C,[8,9] but daytime SOREMPs are not necessarily specific for this diagnosis. Up to 48% of adolescents can have at least one SOREMP, and 16% had two SOREMPS based on normative data.[10] In children younger than 5 y, normative MSLT results have not been published, thus limiting the interpretation of the MSLT at younger ages. Nevertheless, the MSLT is still considered the gold standard for confirming N+C in children in the International Classification of Sleep Disorders, 3rd Edition (ICSD-3).[11]

The nocturnal PSG has been considered less helpful in diagnosing N+C, but recent research suggests that very early occurrence of REM sleep may be diagnostically useful. A nocturnal SOREMP (nSOREMP) is defined as an REM sleep period occurring ≤ 15 min after the onset of sleep on an overnight PSG. In adults, an nSOREMP has high specificity (ranging from 97.5–99.6%) for N+C or narcolepsy with hypocretin deficiency.[12] This high specificity has contributed to modifications in the newly updated ICSD-3.[11] As in the previous edition, the manual specifies that diagnosis of N+C (now known as narcolepsy type 1) requires at least 3 mo of irrepressible need for sleep or daytime lapses into sleep, cataplexy, and a mean sleep latency of ≤ 8 min and two or more SOREMPs on the MSLT; however, the
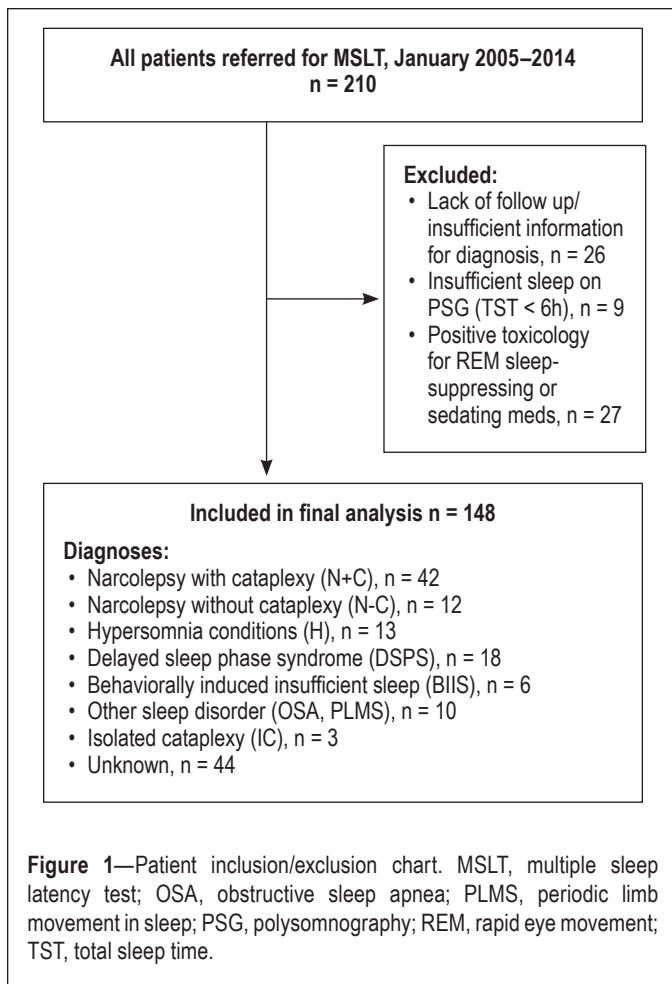
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┌─────────────────────────────────────┐
│  All patients referred for MSLT,     │
│       January 2005–2014              │
│             n = 210                  │
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                │
                │        ┌──────────────────────────┐
                │        │ Excluded:                │
                │───────▶│ • Lack of follow up/     │
                │        │   insufficient information│
                │        │   for diagnosis, n = 26  │
                │        │ • Insufficient sleep on  │
                │        │   PSG (TST < 6h), n = 9  │
                │        │ • Positive toxicology    │
                │        │   for REM sleep-         │
                │        │   suppressing or         │
                │        │   sedating meds, n = 27  │
                ▼        └──────────────────────────┘
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Included in final analysis n = 148

Diagnoses:
• Narcolepsy with cataplexy (N+C), n = 42
• Narcolepsy without cataplexy (N-C), n = 12
• Hypersomnia conditions (H), n = 13
• Delayed sleep phase syndrome (DSPS), n = 18
• Behaviorally induced insufficient sleep (BIIS), n = 6
• Other sleep disorder (OSA, PLMS), n = 10
• Isolated cataplexy (IC), n = 3
• Unknown, n = 44

Figure 1—Patient inclusion/exclusion chart. MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; PLMS, periodic limb movement in sleep; PSG, polysomnography; REM, rapid eye movement; TST, total sleep time.

diagnostic criteria now permit an nSOREMP on the PSG preceding the MSLT to count toward the required two SOREMPs.

nSOREMPs have been described in younger (1–10 y) and older (> 10–18 y) children with N+C,[9,13,14] but we know of no study that determined the sensitivity and specificity of an nSOREMP for diagnosing N+C in a pediatric population. Potentially, if an nSOREMP is a highly sensitive and specific marker for N+C, then the MSLT could be avoided, saving time, lost school and work days, and health care costs. We hypothesized that an nSOREMP is highly specific for the diagnosis of N+C in pediatric populations. To test this question, we performed a retrospective chart review of pediatric patients referred for a PSG and MSLT at Boston Children's Hospital (BCH) for the evaluation of N+C or other hypersomnia conditions.

METHODS

Patients

We reviewed charts of 210 patients aged 6–18 y referred for consecutive PSG and MSLT for the evaluation of N+C or other hypersomnias at BCH between January 2005 and January 2014. Three patients lived outside the United States, and all patients had at least one clinic visit with a board-certified sleep physician at BCH after diagnostic testing to ensure appropriate diagnosis. In cases when a patient had more than one set of PSG and MSLT studies, we analyzed the more recent set of studies. Most patients were referred for EDS, although three patients

presented with possible isolated cataplexy and were tested for N+C. Toxicology screens were performed prior to PSG/MSLT, and children were excluded from this study if the screen revealed medications that can affect sleep latency or REM sleep (e.g., selective serotonin reuptake inhibitor [SSRI]), diphenhydramine, etc.). The local institutional review board at BCH approved the study.

Based on the clinical presentation and PSG and MSLT reports, we categorized patients into ICSD-2 diagnostic categories.[15] The categories included: N+C, narcolepsy without cataplexy (N-C), other hypersomnia conditions (H), delayed sleep phase syndrome (DSPS), behaviorally induced insufficient sleep syndrome (BIISS), other sleep disorders (obstructive sleep apnea and/or periodic limb movements of sleep), isolated cataplexy, and various diagnoses. In the three patients with isolated cataplexy, routine electroencephalography (EEG), magnetic resonance imaging studies of the brain, and electrocardiography were used to evaluate for other etiologies and were normal. Only one of the patients with isolated cataplexy was positive for the HLA DQB1*06:02 haplotype. The "other hypersomnia conditions" category included patients with idiopathic hypersomnia and hypersomnia caused by a medical condition. Patients with no clear ICSD-2 diagnosis after testing and follow-up in a sleep clinic were classified as "various diagnoses." This group mainly included patients with EDS and/or fatigue who did not meet ICSD-2 definitions of hypersomnia; possible causes of symptoms included postviral illness, chronic illness, depression, and/or side effects of medications.

Of the 210 patients who met inclusion criteria, we excluded 26 because of lack of follow-up after PSG/MSLT and insufficient clinical information to confirm a diagnosis, nine because of total sleep time less than 6 h on the PSG prior to MSLT, and 27 because of toxicology results that could affect the PSG or MSLT (Figure 1). The remaining 148 individuals included patients with N+C (28.4%), N-C (8.1%), other hypersomnia conditions (9.5%), DSPS (12.2%), BIISS (4.1%), other sleep disorders (6.8%), and isolated cataplexy (2%). Patients who did not meet an ICSD-2 code were included in the various diagnoses category (29.1%). The patient sample included 62.8% Caucasians, 14.9% African Americans, 2.7% Asians, 3.4% Hispanic, and 5.4% reported as "other". Race data were unavailable for 10.8% of the sample population; 53% of the sample was male and 47% female.

Diagnostic Testing

The PSG and MSLT studies were performed in accordance with American Academy of Sleep Medicine (AASM) practice parameter specifications[16] using Biologics Sleep Scan Vision 2 or Natus Sleep Works software (Natus Medical Inc., San Carlos, CA, USA). Per our laboratory policy, patients stopped any REM sleep-suppressing medications and were asked to maintain a regular sleep schedule for 2 w prior to the study date. The MSLT consisted of five 20-min nap opportunities at 10:00, 12:00, 14:00, 16:00, and 18:00. Dedicated scoring technicians at BCH scored the sleep architecture, respiratory and movement events, and arousals using AASM criteria,[17] and board-certified sleep physicians at BCH reviewed and interpreted the recordings.

Evaluations

We reviewed the medical records of each patient and analyzed the clinical, PSG, and MSLT data. Measures included (1) Clinical: age, race, sex, sleep clinic visit after testing (yes/no), presenting symptoms, habitual bedtime, HLA typing; (2) MSLT: average sleep latency, number of SOREMPs; (3) PSG: lights-off time, total sleep time, sleep efficiency, sleep onset latency (SOL), sleep maintenance, wake after sleep onset (WASO), arousal index (AI), number of awakenings from sleep, nSOREMP (yes/no), REM SOL, periodic limb movement index (PLMI), apnea-hypopnea index, and percentage of stage N1, N2, N3, and REM sleep; (4) Drug testing: presence of positive drug screen for sedating medications and/or SSRI. In addition, we calculated the difference between home bedtime (specified from chart review) and time of lights out on the PSG study.

HLA testing always included the DQB1 and DRB1 loci and was performed by the Tissue Typing Laboratory at Brigham and Women's Hospital (Boston, MA, USA) using polymerase chain reaction sequence specific oligonucleotide techniques. HLA positivity was defined as positive results for DQB1*06:02 alone. 24 (39.3%) of these HLA+ patients also carried DRB1*15:01 and/or DRB1*15:03. HLA typing was classified as "unknown" when results were unavailable in the medical record. In our sample, 61 patients (41.2%) had positive HLA results, 51 had negative results (34.5%), and 36 had no HLA testing or results were not reported in the medical record (24.3%).

Statistical Analysis

We inspected data for normality using histograms and skew statistics and report data as means (standard deviation) or medians (minimum, maximum) depending on the normality of data distribution. Because some diagnostic categories contained few patients, we combined patients into four major groups: N+C, N-C, H, and Other (DSPS, other sleep disorders, BIISS, isolated cataplexy, various diagnoses). We used one-way analysis of variance (ANOVA) to compare continuous measures between diagnostic groups for normative data and the Kruskal-Wallis test for similar comparisons with data that had even a marginally skewed distribution. For statistically significant outcomes, we further conducted *post hoc* pairwise tests with Tukey Honestly Significant Difference tests or Mann-Whitney U tests accordingly. We used Spearman correlation coefficients to examine the strength of linear relationships between age and nocturnal REM latency as well as number of SOREMPs on the MSLT and nocturnal REM latency. Last, we analyzed the number of SOREMPs and the presence or absence of an nSOREMP using a 5×2 contingency table and Fisher exact test. Significance is reported at $P < 0.05$, two-sided. We analyzed all statistics using SPSS version 19 (Armonk, NY: IBM Corporation®).

RESULTS

Clinical characteristics of patients in the collapsed diagnostic categories are listed in Table 1. Patients in the hypersomnia (H) group were older (median age 16 y) than all other groups (P's < 0.05) and had a higher body mass index than the Other group (P = 0.001) on *post hoc* testing. We did not detect

differences in sex (P = 0.6) between groups. There were 75.7% of all patients who had HLA typing, and HLA positivity was most frequent in the N+C group (85.7%). In the N+C group, two patients had negative HLA results, and the remainder had no HLA data.

SOL on the PSG differed across the four groups (P's < 0.0001; Table 1), and in pairwise comparisons, patients with N+C had shorter SOL than patients in the H and Other groups (all P's ≤ 0.003). SOL appeared shorter in the N+C group compared to the N-C group (P = 0.04). Patients with N-C had SOL similar to that of the H and Other groups. The short SOL of N+C patients were probably not related to circadian factors because all groups were similar in the difference between reported bedtime and lights out on the PSG. This propensity for rapid transitions into sleep among the N+C group was also apparent in the daytime; patients with N+C had shorter median sleep latencies on MSLT than those in the N-C, H, or Other groups (Kruskal-Wallis ANOVA testing P < 0.0001, and P's < 0.002 on pairwise comparisons).

N+C patients had much shorter nocturnal REM sleep latencies than the other groups (P < 0.0001). In pairwise comparisons, patients with N+C had shorter nocturnal REM sleep latencies than patients in the H and Other groups (P's ≤ 0.003, Figure 2), but the difference with the N-C group did not reach statistical significance (P = 0.08). The nocturnal REM sleep latencies of patients with N-C were shorter than the Other group (P = 0.006) but similar to the H group (P = 0.1). Nocturnal REM sleep latencies did not correlate with age.

An nSOREMP (REM sleep within 15 min of sleep onset) was far more common in the N+C group compared to all other groups (P < 0.0001). Within the N+C group, 23 patients (54.8%) had nSOREMPs compared to just one patient (8.3%) in the N-C category, and two patients (2.5%) in the Other group. Thus, the specificity of an nSOREMP for detecting N+C among all patients referred for PSG/MSLT testing was high at 97.3% (95% CI: 92.2–99.4%), though the sensitivity was moderate at 54.8% (95% CI: 38.7–70.2%). Overall, the positive predictive value (PPV) of a positive nSOREMP for the diagnosis of N+C was 88.5% (95% CI: 69.8–97.4%). The diagnostic accuracy improved slightly when a patient had both an nSOREMP and positive HLA results: specificity 97.5% (95% CI: 91.4–99.6%), sensitivity 55.3% (95% CI: 38.3–71.4%), and PPV of 91.3% (95% CI: 71.9–98.7%).

We further investigated whether the diagnostic accuracy of an nSOREMP would improve in subgroups of patients with N+C. Though we did not have Tanner staging to confirm pubertal status, we looked at a subgroup of 25 children age 10 y or younger to determine if an nSOREMP would be more useful in children younger than the average age of puberty.[18] In this subgroup, an nSOREMP had a sensitivity of 37.5% (95% CI: 15.3–64.5%) and specificity of 96.7% (95% CI: 82.7–99.4%).

We carefully reviewed the clinical information of the two patients with nSOREMP in whom neither N+C nor N-C was diagnosed. One was a 10-y-old boy, otherwise healthy, who presented with daytime sleepiness and was positive for HLA DQB1*06:02, but had no cataplexy, sleep paralysis, or hypnogogic hallucinations. His mean sleep latency on the MSLT was 10.8 min and he slept in 4/5 naps without any SOREMPs. The second patient was a 17-y-old woman with a diagnosis of

Table 1—Polysomnography and multiple sleep onset latency characteristics of patient groups.

	N+C (n = 42)	N-C (n = 12)	H (n = 13)	Other (n = 81)	P
Patient characteristics					
Age (y)	13 (6,20)	14.5 (6,17)	16 (14,17)	13 (4,18)	< 0.0001
BMI	23.7 (13.8,41.4)	22 (15.2,28)	25 (21.2,37.3)	20.2 (14.2,40)	0.006
Sex (% female)	25 (59.5)	5 (41.7)	8 (57.1)	32 (39.5)	0.13
+HLA (%)	36 (85.7)	8 (66.7)	3 (21.4)	14 (17.3)	< 0.0001
Nocturnal PSG					
Total sleep time (min)	520.4 (62.1)	549.3 (48.2)	541.8 (56.5)	518.4 (59.2)	0.24
Sleep efficiency (%)	87.4 (7.8)	91.5 (3.9)	88 (8.6)	86.4 (8.1)	0.21
Sleep onset latency	5.3 (0,61.5)	11.1 (0,59)	12.8 (0,98.9)	16.4 (0,113)	< 0.0001
Wake after sleep onset (WASO) (min)	66.7 (43.3)	24.8 (16.9)	50.5 (41.8)	52.3 (46.7)	0.03
Sleep maintenance (%)	88.4 (7.4)	88.2 (25)	91.3 (7.2)	89.7(11.5)	0.8
Number of awakenings	23.9(12.2)	16 (7.9)	10 (6.1)	12.5 (8.9)	< 0.0001
Arousal Index	9.6 (5.9)	8.1 (5.6)	8.0 (4.2)	7.2 (4.9)	0.07
REM sleep latency	6.5 (0,243)	70.5 (1.5,135)	113 (52.5,192)	104.5 (3.5,315)	< 0.0001
nSOREMP (%)	23 (54.8)	1 (8.3)	0	2 (2.5)	< 0.0001
Stage N1 (%)	12 (7.4)	6.6 (3.5)	7.8 (2.2)	6.3 (4.6)	< 0.0001
Stage N2 (%)	42 (8.8)	44 (10.6)	50 (7.9)	46.1 (11.4)	0.07
Stage N3 (%)	19.4 (8.7)	20.5 (9.4)	15.7 (7.3)	24.5 (11.6)	0.007
Stage REM (%)	26.5 (6.7)	29 (5.4)	26.4 (6.7)	23.1 (5.8)	0.002
MSLT					
Mean sleep latency (min)	1.7 (0.5,12.8)	4.8 (1.8,17.7)	6 (2.6,9)	16.3 (5,20)	< 0.0001
Number of SOREMPs on MSLT	5 (1,5)	3 (2,5)	0 (0,3)	0 (0,4)	< 0.0001

We collapsed diagnoses into four categories: narcolepsy with cataplexy (N+C), narcolepsy without cataplexy (N-C), other hypersomnias (H), and Other (patients with DSPS, BIIS, isolated cataplexy, and various diagnoses). Age, BMI (body mass index), nocturnal rapid eye movement (REM) sleep latency, mean sleep latency and number of sleep onset REM periods (SOREMPs) are presented as medians and (min, max). HLA positivity is defined as positive results for DQB1*06:02 alone or DQB1*06:02 plus DRB1*15:01 and/or DRB1*15:03 (reported as % positive within group). N+C patients had shorter REM sleep latencies and higher frequency of nocturnal SOREMPs (nSOREMPs) than all other groups. N+C patients also had more awakenings and N1 sleep on PSG and shorter sleep latencies on PSGs and MSLTs than all other groups. MSLT, multiple sleep latency test; PSG, polysomnography.

juvenile absence epilepsy, mild obstructive sleep apnea, and daytime sleepiness. She had an ambulatory EEG (21 h) that showed generalized fast spike waves with brief eyelid fluttering but there was no clinical evidence of atonic seizures or other behaviors that could resemble cataplexy. She was negative for HLA DQB1*06:02, and her MSLT showed a mean sleep latency of 16 min and two SOREMPs. She was treated for her mild obstructive sleep apnea and epilepsy but continued to experience significant daytime sleepiness and was eventually started on stimulants.

We further analyzed the relationships between nSOREMPs and SOREMPs on the MSLT. The number of SOREMPs on the MSLT was strongly related to the presence of an nSOREMP (Figure 3). There were 73% of patients with an nSOREMP who had four or five SOREMPs on MSLT compared to 13% of patients without an nSOREMP (Fisher exact test, P < 0.0001). Conversely, the frequency of having an nSOREMP increased with the number of MSLT SOREMPs; an nSOREMP occurred in only 0–1% of patients with 0 or 1 MSLT SOREMP, but it occurred in 36% of patients with two SOREMPs and in 54% of patients with four or five SOREMPs. Similarly, shorter nocturnal REM sleep latencies correlated with a higher number of MSLT SOREMPs (r = −0.47, P < 0.0001).

Last, we examined markers of nocturnal sleep disruption and found significant differences in the percentage of stage N1 sleep, WASO, and the number of awakenings on the study night between the four groups (ANOVA P's < 0.03). The N+C group had more awakenings through the night than the H group and the Other group (P's < 0.0001), and the difference between the N+C and N-C groups trended toward significance (P = 0.05). The N+C group had more WASO than the N-C group (P = 0.02) but not compared to the other two groups (P's > 0.3). The N+C group also had more stage N1 sleep than patients in the Other group (P < 0.0001) and the N-C group (P = 0.03) but not those in the H group (P = 0.11). Sleep maintenance, sleep efficiency, and arousal index did not differ between groups (ANOVA P's ≥ 0.07).

DISCUSSION

We examined the diagnostic accuracy of an nSOREMP for identifying N+C in a pediatric population and found that an nSOREMP has a specificity of 97.3% but a sensitivity of 54.8%. Also, nSOREMPs are much more common in N+C than in N-C.

The specificity of an nSOREMP in our population of children with N+C is consistent with the adult literature.[12] Andlauer et al. reported a comparable specificity of 95.4% (95% CI: 90.4–98.3%) and sensitivity of 57.4% (95% CI: 48.1–66.3%) in a population of adult sleep clinic patients undergoing PSGs and MSLTs. The high specificity of this finding in both the

adult and pediatric populations suggests that an nSOREMP is a stable trait in N+C and further supports its inclusion in the new ICSD-3 definition of N+C.[11] An nSOREMP is also part of the new definition for N-C, but because an nSOREMP is rare in these patients, this is unlikely to have much practical impact. However, we detected nSOREMPs in two patients with diagnoses other than narcolepsy, but in neither case would the presence of an nSOREMP have changed the diagnosis to narcolepsy based on the ICSD-3 criteria because these patients lacked key indicators of narcolepsy. One of these patients had no SOREMPs on the MSLT, and the other had a mean sleep latency > 8 min. Narcolepsy can evolve over time, and it is possible these patients will develop more characteristic symptoms of narcolepsy as they age.[19,20]

The sensitivity of an nSOREMP is moderate at 57.4% for the diagnosis of N+C, which means that more than 40% of patients would be missed with this marker alone. The sensitivity is even lower in children age 10 y or younger, at 37.5%. The modest sensitivity of an nSOREMP in both children and adults highlights the importance of a MSLT for diagnosis if there is no nSOREMP. However, the high specificity suggests that if a patient has classic symptoms of N+C and an nSOREMP, a clinician could be more than 90% certain that the patient has N+C, taking into account the reported confidence intervals. In pediatric patients with N-C, an nSOREMP is quite rare and has a sensitivity of only 4%. The cause of this striking difference in frequency of nSOREMPs between N+C and N-C is unclear, but it may reflect more severe loss of hypocretin neurons or additional central biochemical alterations in people with N+C.[21,22] It is also possible that N-C is more etiologically heterogeneous than N+C, resulting in less specific symptoms
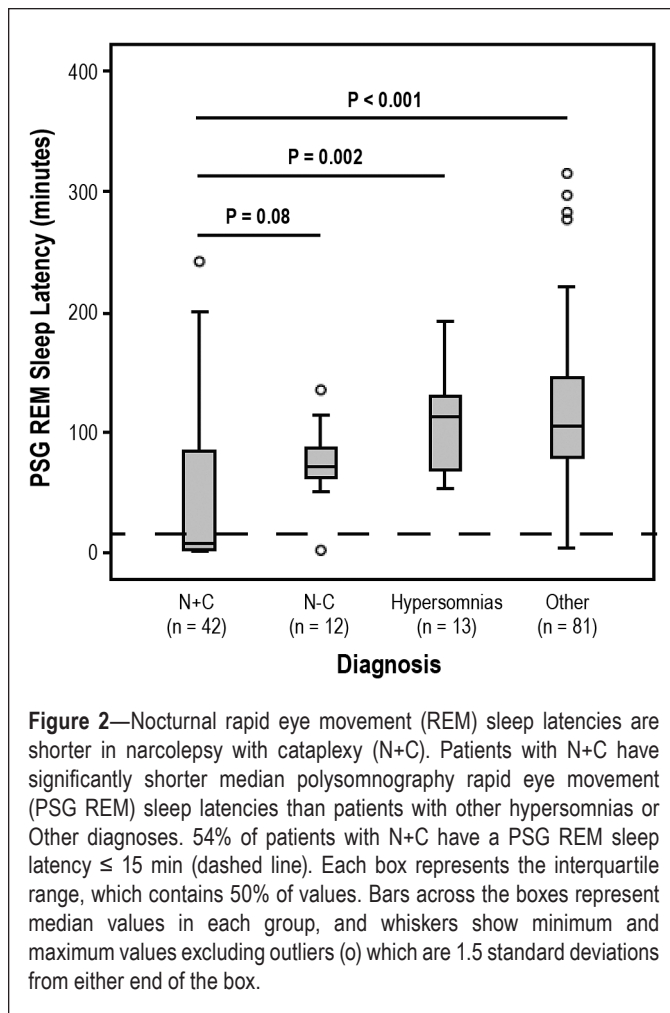
Figure 2—Nocturnal rapid eye movement (REM) sleep latencies are shorter in narcolepsy with cataplexy (N+C). Patients with N+C have significantly shorter median polysomnography rapid eye movement (PSG REM) sleep latencies than patients with other hypersomnias or Other diagnoses. 54% of patients with N+C have a PSG REM sleep latency ≤ 15 min (dashed line). Each box represents the interquartile range, which contains 50% of values. Bars across the boxes represent median values in each group, and whiskers show minimum and maximum values excluding outliers (o) which are 1.5 standard deviations from either end of the box.
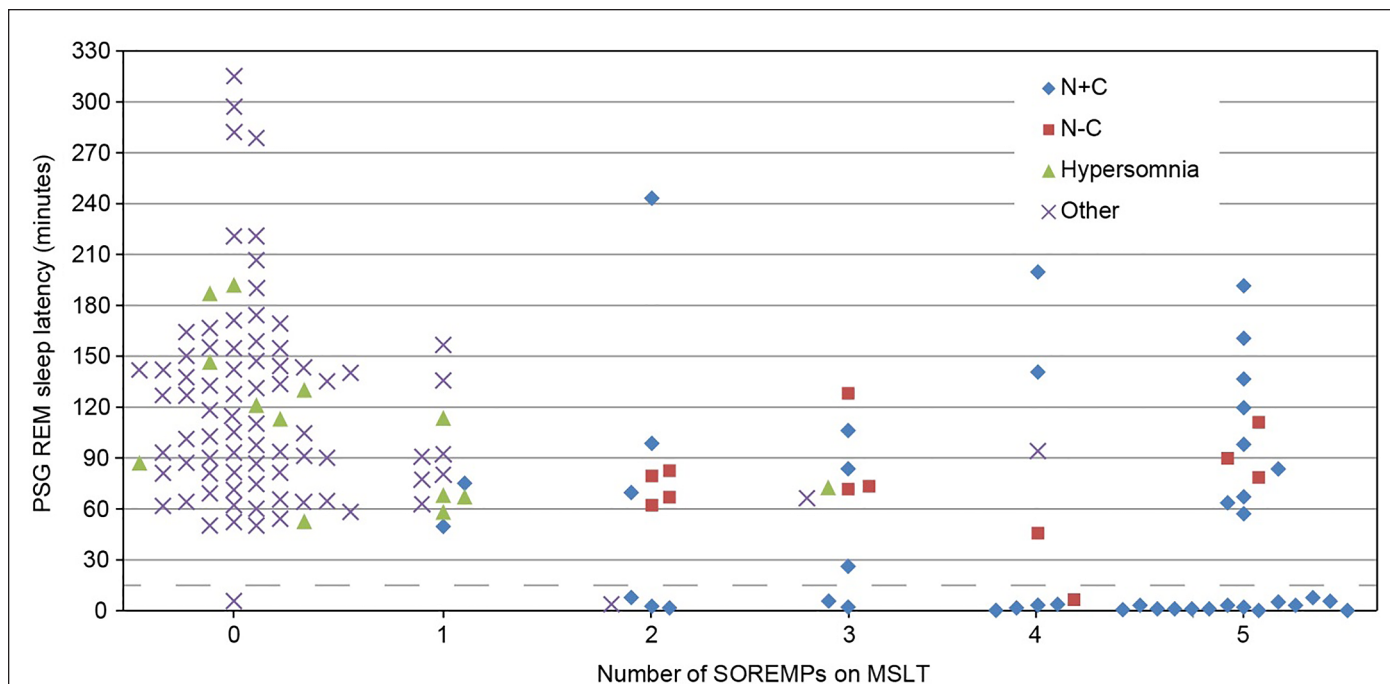
Figure 3—Nocturnal rapid eye movement (REM) sleep latency is strongly associated with the number of sleep onset rapid eye movement sleep periods (SOREMPs) on multiple sleep latency tests (MSLT). Polysomnography (PSG) REM sleep latencies are in the normal range in patients with only 0 or 1 MSLT SOREMPs, but over half of all patients with 4 or 5 SOREMPs have nSOREMPs, with REM sleep latencies ≤ 15 min. nSOREMPs predominantly occur in patients with N+C.

and signs. Certainly, the lack of reliable biomarkers contributes to the challenges of accurately diagnosing N-C.[23]

We found that across all diagnoses, the presence of an nSOREMP on the PSG was strongly related to the number of SOREMPs on the MSLT. Most of our patients with nSOREMPs had four or five MSLT SOREMPs, and short nocturnal REM latencies were strongly associated with more MSLT SOREMPs. From a physiological perspective, these findings suggest that rapid transitions into REM sleep at night are driven by the same altered REM sleep physiology that gives rise to REM sleep in daytime naps. From a clinical perspective, the ICSD-3 criteria to include an nSOREMP with the MSLT SOREMP tally seems superfluous because nearly all individuals with an nSOREMP have more than two MSLT SOREMPs and inclusion of the nSOREMP in the overall tally is unlikely to alter the diagnosis. Similarly, in the study by Andlauer et al., all subjects with an nSOREMP had at least two daytime SOREMPs and mean sleep latency ≤ 8 min.[20] Still, these observations suggest that in the right clinical context, the presence of an nSOREMP may permit reduction of the duration of the MSLT to four naps instead of five, assuming a total of two SOREMPs (including the nSOREMP) have occurred. Such a reduction in the duration of the MSLT would provide adequate diagnostic accuracy and meaningful clinical information about the degree of sleepiness during the daytime hours.

Patients with N+C also demonstrated more sleep disruption than other groups. Specifically, patients with N+C had more awakenings during the night than other groups, though their WASO was not significantly longer in all comparisons. However, other sleep measures such as total sleep time, sleep efficiency, sleep maintenance, and arousal index were comparable between groups. Similar to prior research,[24,25] we detected differences in sleep architecture between the N+C and N-C groups on measures such as SOL, WASO, number of awakenings, and percentage of N1 sleep, which suggests less stable sleep in N+C patients.

Our study has several limitations. First, we included patients in whom N+C had been diagnosed based on clinical symptoms and diagnostic testing rather than hypocretin testing. Two patients in whom N+C had been diagnosed had only one SOREMPs on MSLT, and another patient with N+C had an average sleep latency on MSLT > 8 min. N+C was diagnosed in these patients because they had unambiguous and chronic cataplexy with recurrent daytime lapses into sleep that met the ICSD-2 criteria. In addition, not all patients with N+C were positive for HLA DQB1*06:02. However, we think that the heterogeneity of our population is more generalizable to other clinical centers. Second, we have small populations in some of the diagnostic categories that required us to group patients into larger diagnostic categories for analysis. In future studies, larger sample sizes from multiple sleep centers will be needed to minimize type 1 and type 2 errors. Third, scorers and readers varied across studies, which could affect the scoring of REM sleep and nSOREMPs. In adults, the scoring of REM sleep is highly reliable across scorers[26,27] but this has not been replicated in pediatric studies. Last, patients in the Hypersomnia group were generally older than those in the other groups, and this might affect sleep physiology. We think this is unlikely to be a concern as sleep onset REM sleep periods would be expected to subside by 3 mo of age[28] and the youngest child in the study was 4 y of age. Furthermore, we found no associations between age and nocturnal REM sleep latencies in our study population. Still, sleep physiology may differ in prepubertal patients, and future studies should include younger children as normative data in this group are scant.

In conclusion, we found that in pediatric patients referred for a PSG and MSLT, the presence of an nSOREMP has a high specificity and positive predictive value for N+C and is of great diagnostic utility. If an nSOREMP is present, then N+C is highly likely and some clinicians may opt to skip the MSLT. However, this decision must be balanced against some practical considerations because a sleep technician and sleep physician would need to determine quickly if an nSOREMP is present and whether to proceed with the MSLT. Importantly, although the MSLT requires significant time and expense, it also provides objective information on the severity of REM sleep dysregulation, daytime sleepiness, and times of greatest sleep propensity. Such information is often clinically informative to help plan scheduled naps, the timing of stimulants, and safety counseling on activities such as driving. Thus, our findings on the utility of nSOREMPs in children, coupled with recent, similar data in adults, have important implications for the clinical diagnosis of N+C. Furthermore, the presence of an nSOREMP in conjunction with MSLT results provides clinically useful information on the severity of N+C.

DISCLOSURE STATEMENT

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