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Original Article

Sleep-stage transitions during polysomnographic recordings as diagnostic features of type 1 narcolepsy

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ABSTRACT

Objective: Type 1 narcolepsy/hypocretin deficiency is characterized by excessive daytime sleepiness, sleep fragmentation, and cataplexy. Short rapid eye movement (REM) latency (≤15 min) during nocturnal polysomnography (PSG) or during naps of the multiple sleep latency test (MSLT) defines a sleep-onset REM sleep period (SOREMP), a diagnostic hallmark. We hypothesized that abnormal sleep transitions other than SOREMPs can be identified in type 1 narcolepsy.

Methods: Sleep-stage transitions (one to 10 epochs to one to five epochs of any other stage) and bout length features (one to 10 epochs) were extracted from PSGs. The first 15 min of sleep were excluded when a nocturnal SOREMP was recorded. $F_{0.1}$ measures and receiver operating characteristic curves were used to identify specific (≥98%) features. A data set of 136 patients and 510 sex- and age-matched controls was used for the training. A data set of 19 cases and 708 sleep-clinic patients was used for the validation.

Results: (1) ≥5 transitions from ≥5 epochs of stage N1 or W to ≥2 epochs of REM sleep, (2) ≥22 transitions from ≥3 epochs of stage N2 or N3 to ≥2 epochs of N1 or W, and (3) ≥16 bouts of ≥6 epochs of N1 or W were found to be highly specific (≥98%). Sensitivity ranged from 16% to 30%, and it did not vary substantially with and without medication or a nocturnal SOREMP. In patients taking antidepressants, nocturnal SOREMPs occurred much less frequently (16% vs. 36%, $p < 0.001$).

Conclusions: Increased sleep-stage transitions notably from ≥2.5 min of W/N1 into REM are specifically diagnostic for narcolepsy independent of a nocturnal SOREMP.

1. Introduction

Current diagnostic criteria for type 1 narcolepsy (NC) include daytime sleepiness, cataplexy or low hypocretin-1 in the cerebrospinal fluid (CSF), and a positive multiple sleep latency test (MSLT). Polysomnographic (PSG) features include an instability of the sleep–wake cycle together with daytime sleepiness, short sleep latency, fragmented nocturnal sleep, and abnormal rapid eye movement (REM) sleep with a shortened REM sleep latency during nocturnal sleep and daytime naps, and events of dissociated REM sleep [1–3]. The disease is caused by the loss of approximately 50–70,000 hypocretin-producing neurons in the hypothalamus, resulting in negligible levels of hypocretin-1, a wake-promoting peptide, in the CSF [4–8]. The lack of hypocretin is causative to the disorder as animals mutated for hypocretin receptors or lacking the hypocretin ligand have narcolepsy [9,10]. Although this is not fully established, the cause of the hypocretin cell loss in humans is almost certainly of autoimmune origin. Indeed, the disease is strongly associated with human leukocyte antigen (HLA) DQB1*06:02 and other immune polymorphisms, and its onset is often triggered by upper airway infections such as influenza [11].

Historically, rapid transitions from sleep onset into REM sleep (so-called sleep-onset REM periods or SOREMPs, defined as REM sleep latency of ≤15 or 20 min) were first observed during nocturnal

Abbreviations: CSF, cerebrospinal fluid; FN, false negatives; FP, false positives; HLA, Human leukocyte antigen; ICSD, International Classification of Sleep Disorders; IH, idiopathic hypersomnia without long sleep time; MSL, mean sleep latency; MSLT, Multiple sleep latency test; NC, narcolepsy type 1; PSG, polysomnography; REM, rapid eye movement; ROC, receiver operating characteristic; SOREMP, sleep-onset REM period; TN, true negatives; TP, true positives.

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sleep in the 1960s [12,13]. Because of low sensitivity, however (~40–50%), it could not be used diagnostically, and the MSLT, a test where four to five daytime naps are administered, was used to give more SOREMP opportunities. The MSLT gained widespread acceptance as a diagnostic test, and it was shown to be ~95% specific and ~95% sensitive for type 1 narcolepsy when a mean sleep latency (MSL) of ≤8 min and ≥2 SOREMPs (REM latency ≤15 min) were observed during daytime naps, a criteria used in the International Classification of Sleep Disorder Second Edition (ICSD-2) [14]. More recently, because a nocturnal SOREMP was found to be highly specific (~99%) for narcolepsy [2,15] and a PSG is required before the MSLT to exclude sleep deprivation or other sleep disorders, nocturnal SOREMPs have been added back as a diagnostic criteria in the new International Classification of Sleep Disorders Third Edition, the ICSD-3 [16].

Considering the above, the diagnosis of type 1 narcolepsy is currently based on documenting two or more of the following: Clinical observation of cataplexy, low CSF hypocretin-1, or/and a diagnostic PSG-MSLT. A PSG-MSLT is considered to be diagnostic for narcolepsy when MSL is ≤8 min during the four to five daytime naps of the MSLT, and a REM sleep latency of ≤15 min is observed at least twice when falling asleep at night and during MSLT naps [16]. The PSG-MSLT must be performed in a sleep laboratory, most notably because a valid MSLT mandates that the subject does not sleep between daytime naps. In addition, the patient must have been shown to have regular, sufficient sleep during nighttime hours before testing (shift workers are particularly at risk of false positives) [17], and the patient has to have been free of any stimulant or antidepressant treatment for at least a week. Although the sensitivity and specificity of this revised ICSD-3 PSG-MSLT criteria have not been formally analyzed, they are likely to remain similar to those of the ICSD-2 MSLT alone. In a recent analysis of several thousand patients with type 1 narcolepsy, only three of over 1000 subjects had a SOREMP at night and only one SOREMP during the MSLT [18]. As specificity for a SOREMP alone is extremely high (99%), the overall specificity of the revised criteria is also unlikely to change significantly.

In continuation of the study by Andlauer et al. [2], this work aims at identifying sleep transition features in nocturnal sleep that could be an indicative of type 1 narcolepsy, with the ultimate goal of using nocturnal PSG alone to diagnose narcolepsy. Prior studies have shown abnormal sleep–wake transitions during nocturnal sleep in narcoleptics [1,19–23]. Specifically, Liu et al. [23] investigated the diagnostic value of transitions to REM sleep in nocturnal PSGs as well as in MSLT for narcolepsy types 1 and 2. This study not only investigates transitions to REM sleep but also performs an extensive search in various sleep transitions between all sleep stages and thresholds on the total number hereof to identify specific features, which can identify narcolepsy in a clinical setting. This study postulates that by extracting such features from the hypnogram of a nocturnal PSG and by combining those with the SOREMP feature, the sensitivity of identifying narcolepsy can be raised while maintaining the high specificity.

2. Materials and methods

2.1. Subjects and recordings

Two data sets were used in this study; a training data set that was used to identify potential diagnostic features, and a validation data set that was used to confirm findings in a clinical setting. Because our goal was to identify highly specific indices, the two data sets were oversampled in non-narcolepsy subjects. Patients who were diagnosed with type 1 narcolepsy met ICSD-3 criteria (narcolepsy with cataplexy/hypocretin-deficient narcolepsy) [16]. All had clear cataplexy, and they were HLA-DQB1*06:02 positive. In cases where CSF hypocretin had been measured, levels were below 110 pg/ml, consistent with hypocretin deficiency. All cases had a positive MSLT, defined as MSL of ≤8 min and ≥2 SOREMPs during naps or at nighttime sleep onset.

The training data set included 136 narcolepsy type 1 patients diagnosed at the Stanford Sleep Clinic as well as PSGs from two sodium oxybate drug trials (baseline sleep studies, SXB15 with 45 sites in Canada, USA, and Switzerland, and SXB22 with 44 sites in Canada, Europe, and the USA) conducted by Orphan Medical, now named Jazz Pharmaceuticals [24,25]. In SXB15, patients were allowed to be on a stable dose of stimulant [24], whereas in SXB22, both modafinil and anticataplectic antidepressants were allowed at stable doses [25]. In the combined drug trial baseline sample used in this study, which only included patients with clear cataplexy, 39% took antidepressants, whereas 79% took centrally acting stimulants. The training data set also included 510 sex- and age-matched control subjects obtained from the Wisconsin sleep cohort [26]. Samples were matched for age and sex using the nearest-neighbor-matching function from the MatchIt package for R, with a control/case ratio of 4, and a number of standard deviations of the distance measure within which to draw control units (caliper) set at 0.25 [27]. Thirty controls (5.8%) were working rotating or graveyard shifts. As for patients, controls were allowed to take usual medications such as over-the-counter antihistamine and pain-relieving medication. Antidepressants such as serotonin-specific reuptake inhibitors were taken by approximately 22%, whereas stimulants, mostly methylphenidate, were used in <2% of the control subjects. Although we noted that the use of therapy was different in cases versus controls, this was considered acceptable as doses were stable, and we also separately explored the effects of these medications on our results. The validation data set consisted of 727 patients evaluated at the Stanford Sleep Clinic. Nineteen were diagnosed with type 1 narcolepsy (untreated when tested), and the rest were non-narcolepsy patients, most notably patients with sleep apnea. This sample has been described elsewhere [2,28]. All evaluations included a comprehensive medical and medication history, nocturnal PSG, and, for narcolepsy cases, a PSG-MSLT. Demographic and PSG data for the two data sets are summarized in Table 1.

2.2. Extraction and definition of features under study

Features evaluated in this study were all extracted from manually scored hypnograms, as would be in a typical clinical sleep study. In older recordings, stage S4 was combined with S3, and it was defined as N3, according to the most recent scoring rules. Transitions between stages were computed and classified into eight feature groups: (1) transitions to REM sleep, (2) transitions to N3 sleep, (3) transitions to N2 sleep, (4) transitions to N1 sleep, (5) transitions to wakefulness, (6) transitions to N1 or wakefulness, (7) transitions to N2 or N3, and (8) number of sleep and wake bouts. Figure 1 illustrates the transition feature groups 1–7, where the total number of any of the specified transitions was counted for each subject. For feature group 1, for instance, the number of transitions from at least one to 10 epochs of any stage (N3, N2, N1, W, N2/N3, N1/W) to at least one to five epochs of REM sleep was computed, yielding 300 subfeatures; the first feature in this group is thus the total number of transitions from at least one epoch of N3 to at least one epoch of REM sleep; the next feature is the total number of at least two epochs of N3 to at least one epoch of REM sleep, and so forth. We wanted to do an exclusive search, and the maximum number of 10 epochs before and five epochs after the transition was chosen as none of the final features selected had numbers higher than these, and hence we had reached the boundary. For feature group 8, the total number of bouts of at least two to 10 epochs of N1 or

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