Clinical Neurophysiology 127 (2016) 2812–2819

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Decreased sleep stage transition pattern complexity in narcolepsy type 1

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ARTICLE INFO

Article history:
Accepted 31 May 2016
Available online 8 June 2016

Keywords:
Sleep stage transitions
Markov process
Entropy rate
Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnia
Subjective hypersomnolence

HIGHLIGHTS

- Narcolepsy type 1 might exhibit distinctive sleep stage sequence organization and complexity.
- The sleep stage transition pattern in type 1 narcolepsy is different from other hypersomnolences.
- R-to-N2 transition probability <0.15 has high sensitivity and specificity for narcolepsy type 1.

ABSTRACT

Objective: To analyze the complexity of the nocturnal sleep stage sequence in central disorders of hypersomnolence (CDH), with the hypothesis that narcolepsy type 1 (NT1) might exhibit distinctive sleep stage sequence organization and complexity.
Methods: Seventy-nine NT1 patients, 22 narcolepsy type 2 (NT2), 22 idiopathic hypersomnia (IH), and 52 patients with subjective hypersomnolence (sHS) were recruited and their nocturnal sleep was polysomnographically recorded and scored. Group between-stage transition probability matrices were obtained and compared.
Results: Patients with NT1 differed significantly from all the other patient groups, the latter, in turn, were not different between each other. The individual probability of the R-to-N2 transition was found to be the parameter showing the difference of highest significance between the groups (lowest in NT1) and classified patients with or without NT1 with an accuracy of 78.9% (sensitivity 78.5% and specificity 79.2%), by applying a cut-off value of 0.15.
Conclusions: The main result of this study is that the structure of the sleep stage transition pattern of hypocretin-deficient NT1 patients is significantly different from that of other forms of CDH and sHS, with normal hypocretin levels.
Significance: The lower probability of R-to-N2 transition occurrence in NT1 appears to be a reliable polysomnographic feature with potential application at the individual level, for supportive diagnostic purposes.

1. Introduction

Narcolepsy type 1 (NT1) is a central disorder of hypersomnolence (CDH) defined by the unique biological evidence of hypocretin-1 deficiency (American Academy of Sleep Medicine, 2014). Indeed, all the other CDHs share with NT1 the chronic sleepiness complaint confirmed by high sleep propensity at the multiple sleep latency test (MSLT), whereas NT1, narcolepsy type 2 (NT2) and, in some cases, the insufficient sleep syndrome are entwined by the frequent occurrence of REM sleep within 15 min from the sleep onset (Marti et al., 2009), defined as sleep onset REM periods (SOREMPs). The dysregulation of REM sleep that characterizes the narcolepsies is mirrored from the clinical standpoint by several REM sleep-related symptoms, such as sleep paralyses and hallucinations, both typically occurring along the transition between wakefulness and sleep, but cataplexy remains the distinctive feature of NT1 (American Academy of Sleep Medicine, 2014).

Abbreviations: CDH, central disorder of hypersomnolence; NT1, narcolepsy type 1; NT2, narcolepsy type 2; IH, idiopathic hypersomnia; sHS, subjective hypersomnolence; MSLT, multiple sleep latency test; SOREMP, sleep onset REM period; TPM, transition probability matrix; H0, zero-memory Markov model entropy rate; H1, first-order Markov model entropy rate.

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http://dx.doi.org/10.1016/j.clinph.2016.05.364
1388-2457/

In the last years, several reports pointed out interesting neurophysiological features that may help in the differential diagnosis of CDHs. Indeed, the occurrence of a SOREMP in the polysomnography of the night before the MSLT shows a low sensitivity but high specificity to identify narcolepsy (Andlauer et al., 2013), and has consequently been re-introduced among the objective criteria in the third International classification of sleep disorders (American Academy of Sleep Medicine, 2014). More detailed analyses of polysomnographic data showed also that NT1 patients typically enter into SOREMPs from non-REM sleep stage 1 both during daytime (Drakatos et al., 2013b; Marti et al., 2009) and nighttime (Drakatos et al., 2013a), a finding that may add information to the endophenotype of the narcolepsy spectrum, but appears to be redundant for basic diagnostic or screening purposes. Conversely, the evidence of high transitional rates in NT1 has linked neurophysiological data, interpreted by means of routinely performed visual scoring, to the underlying state boundary dyscontrol (Broughton et al., 1986; Sorensen et al., 2013); such an approach might be included in potential screening tools, also applicable in the epidemiological setting (Plazzi and Pizza, 2013). We have recently disclosed also that high transitional rates, the occurrence of nocturnal SOREMP, and increased amounts of non-REM sleep stage 1, may act together as objective markers of NT1, with a reliability close to the number of SOREMPs at the MSLT (i.e. yet considered the neurophysiological gold standard) and at the daytime continuous recording (Pizza et al., 2015), which has previously been reported to be another sensitive and specific diagnostic tool (Pizza et al., 2013b). However, the previous analyses evaluated the stage sequence exclusively across the sleep onset period, and no data are available on the relation between states in the whole major sleep period.

The aim of this new study was to analyze, in detail, the time structure and complexity of the nocturnal sleep stage sequence and the transitions between them, also by applying the Markov chain model. Based on the findings of the previous literature, we hypothesized that NT1, distinguished from all other CDHs by the deficit in hypocretin-1, might exhibit different sleep stage sequence organization and complexity.

2. Material and methods

2.1. Patients

Subjects were consecutive drug-naive patients evaluated for complaints of chronic sleepiness (lasting for at least 3 months) from June 2006 to June 2012 at the Outpatient Clinic for Narcolepsy of the Sleep Disorders Center of the Department of Biomedical and Neuromotor Sciences (DIBINEM) of the University of Bologna, and who received a final diagnosis of CDH fulfilling current international diagnostic criteria (American Academy of Sleep Medicine, 2014). For the purpose of the study we applied the following additional inclusion criteria: (1) availability of CSF hypocretin-1 measurement for NT1 diagnosis; (2) evidence of high sleep efficiency (supportive criterion) in the second nocturnal recording for IH diagnosis; (3) exclusion of familial, genetic (e.g. narcolepsy secondary to methylopathies) (Moghadam et al., 2014), and secondary forms (e.g. brain malformations, psychiatric or significant medical comorbidity) for all CDH diagnoses. Finally, we also included a reference group named "subjective HS" (sHS) who were subjects who did not have any clinical or polysomnographic evidence of sleep disturbance and showed normal sleep propensity at the MSLT, despite the clinical complaint of excessive daytime sleepiness, confirmed by the high score at the Epworth sleepiness scale (Johns, 1991).

2.2. Procedures

All patients underwent the following standardized procedures: (1) clinical evaluation by the same expert in sleep medicine (G.P.); (2) subjective sleepiness assessments using the Epworth Sleepiness scale (Johns, 1991); (3) 48-h continuous polysomnography followed by (4) a clinical MSLT with five nap opportunities (Littner et al., 2005), and (5) lumbar puncture and blood drawn whenever possible to assess cerebrospinal hypocretin-1 levels and human leucocyte antigen typing. Our standardized diagnostic algorithm has been previously detailed and included repeated clinical evaluations coupled with extension of nocturnal sleep and nocturnal cardiorespiratory monitoring to rule out psychiatric comorbidity, sleep deprivation, and sleep disordered breathing, respectively, while confirming sleepiness complaint, before hospitalization (Pizza et al., 2013b, 2015).

The 48-h polysomnography performed with an ambulatory device included conventional EEG, bilateral EOG, submentalis and bilateral anterior tibialis EMG, respiratory parameters, and ECG (Iber et al., 2007). During daytime, patients were allowed to sleep whenever they wanted in unscheduled free-running conditions, and a sleep diary was used to identify the major nocturnal sleep period. The reliability of diary reports was verified by reviewing the continuous video recording in the patient room by the board-certified polysomnography technician (S.V.) before scoring the polysomnography and the MSLT (Iber et al., 2007). The study was approved by the local Institutional Review Board and all patients gave written informed consent.

2.3. Sleep architecture analysis

Neurophysiological data recorded during the 48-h polysomnography were first dichotomized in daytime versus nocturnal recordings using sleep diaries and verifying lights off/on timing from the video recording in the patient room.

For this study, sleep stages were scored on consecutive 30-s epochs in nocturnal recordings, following standard criteria (Iber et al., 2007), by a board certified polysomnographic technician (S.V.) who was blind to clinical information; then the raw scoring of each night was exported in an excel file and the number of all transitions between all pairs of different stages was counted (W, N1, N2, N3, REM) as previously detailed (Pizza et al., 2015).

2.4. Group sleep stage transition probability matrices

Sleep stage transition matrices were computed for each group by pooling together all stage transitions observed in all subjects within each group. Subsequently, a 5×5 matrix was obtained for each group; the 25 entries in this matrix were the probabilities of transition from a given state to the next state. For a reliable statistical and structural comparison (see after) of transition matrices, a number of transitions equal to at least 8 times the number of the matrix cells is needed (Jansen and Cheng, 1988). The average total number of stage transitions available for each patient in this study was 119 but for our 25 matrix entries we would have needed at least 200 transitions/patients. For this reason, this analysis was performed on a single matrix per group, with the pooled total group transitions.

We then obtained standardized transition probability matrices (TPMs) containing the probability of stage transition and not its absolute number which allowed the comparison between groups. For example, if the transition from R to N1 occurred 319 times in *N* possible transitions from R to any other stage, then the transition probability in cell [5, 2] of the matrix (i.e., cell in the first row and