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Original Article

Difficult morning awakening from rapid eye movement sleep and impaired cognitive function in delayed sleep phase disorder patients

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ABSTRACT

Objectives: Difficult awakening is a key symptom of delayed sleep phase disorder (DSPD), but no studies have quantified awakening thresholds in a sleep laboratory. This study assessed whether cognitive function was impaired after awakening and whether difficult awakening was associated with specific polysomnographic features such as slow wave sleep stage N3.
Methods: Nine patients with DSPD and nine sex- and age-matched healthy controls were included. Polysomnography was performed at our university hospital from midnight. An alarm clock was activated at 07:00 with sound intensity increasing from 72 to 104 dB. Participants performed a continuous performance test (CPT) the previous afternoon and immediately upon awakening.
Results: Three DSPD patients and zero controls did not wake up to the maximum 104 dB alarm sound; all three patients were in rapid eye movement (REM) sleep when the alarm clock went off (difference in proportions, $P = 0.047$). In patients, CPT reaction time was prolonged in the morning compared to the afternoon [analysis of variance (ANOVA) interaction, $P = 0.01$]. DSPD patients made more omission errors than controls regardless of time of the day (ANOVA main effect, $P = 0.046$).
Conclusion: Difficult awakening from slow wave sleep was not observed. A subgroup of DSPD patients may have a severe problem waking up from REM sleep. DSPD patients may also have a state-like impairment in cognitive function in the morning and a trait-like impairment not depending on time of day, compared to normal sleepers.

1. Introduction

Delayed sleep phase disorder (DSPD) prevalence among high school students may be as high as 8.4% [1], whereas the prevalence in adults may be as low as 0.17% [2].

Some patients with DSPD report extreme difficulty with waking up in the morning, as they do not react to an alarm clock [3]. Patients may be unable to keep a job or have problems completing education because of absence in the morning [4,5].

Whereas difficult morning awakening is a diagnostic criterion (ICSD-2) and highly disabling symptom in DSPD, research on this phenomenon has not yet been conducted [3]. Specifically, it has not been tested whether patients have a different wake-up threshold compared to healthy controls in the morning. Moreover, no studies have explored potential mechanisms for why these patients have difficulties waking up. Most awakenings in healthy subjects follow a rapid eye movement (REM) sleep period [3,5,6]. On the other hand, awakening from slow wave sleep (SWS) may be difficult, often resulting in confusion and impaired arousal [7]. The difficult morning awakening for patients with DSPD could therefore be related to sleep stage [8].

DSPD patients commonly report poor cognitive function when forced to arise early in the morning. Temporarily impaired cognitive function upon awakening is also a characteristic of sleep inertia (SI) [7,9], and its severity has been related to awakening during slow wave sleep (N3) and after reduced total sleep time (TST) [7,10]. Consequently as DSPD patients have considerable amounts of N3 sleep between 06:00 and 08:00 [8], it may be hypothesized that difficult awakening mainly occurs from N3 in patients with DSPD.

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It has been suggested that SI is primarily associated with low arousal (increased reaction time), whereas SI in the context of sleep deprivation also introduces lapses in vigilance (reduced accuracy) [11]. The continuous performance test (CPT) has the capacity to reliably assess both speed and accuracy [12,13], and measures both sustained and transient cognitive control processes that are subserved by brain regions [14] shown to be particularly prone to SI effects [15].

One aim was to quantify the awakening threshold in DSPD patients with an alarm clock. Another hypothesis was that cognitive function would be reduced upon awakening relative to daytime performance in DSPD patients compared to healthy controls. A third hypothesis was that difficult awakenings would be associated with some sleep stage (SWS in particular).

2. Methods

2.1. Participants

Patients were interviewed by physicians experienced with sleep disorders using a semi-structured interview. Nine patients diagnosed with DSPD were included in the study (four males, five females) (mean age, 22.5 ± 2.2 years; range, 18–25). The included patients met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV 307.45) diagnostic criteria for circadian rhythm sleep disorder [16] and the ICSD-2 criteria for DSPD [17].

Nine healthy subjects (four males and five females) (mean age 23.3 ± 2.4 years; range, 18–28) were recruited by posting an announcement on the University's homepage and local campus boards.

Subjects with coexisting other major health problems or regular use of neuroactive drugs the last 4 weeks were not included.

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics.

2.2. Procedure

Participants completed a sleep diary for 14 days and wore an actigraph for the last 7 days before polysomnography (PSG) was recorded for two nights. An ambulatory PSG was done first to minimize the 'first-night effect' [18].

The experimental PSG was performed two days after the initial PSG. Participants came to the sleep laboratory at 14:00, took the CPT at 15:00, and completed psychiatric and sleep-related questionnaires afterwards. The light was dimmed to <200 lux from 18:00. Saliva was sampled for melatonin testing every hour from 19:00 to bedtime at midnight. At exactly 07:00 the following morning, an alarm clock was activated. This custom-made tone generator started at 72 dB sound pressure level, increasing by 2 dB at equal intervals (sound active for 4.4 s with 5 s intervals) until the subject was awake or the 104 dB maximum was reached after 3 min. Two standard personal computer speakers (Sony, SRS-Z510) were placed on each side, ~50 cm from the head. The exact time and dB value at which each person reacted were noted. Subjects who did not react at all to 104 dB alarms were awakened manually. Six minutes after awakening the participants took the same CPT test, with identical instructions as the day before.

2.3. Assessments

2.3.1. Actigraphy

The actigraph (AW4, CamNtech Ltd, Cambridge, UK) recorded 30 s epochs for 7 days prior to the experimental night with medium sensitivity. We used sleep start and sleep end for analyses.

2.3.2. Polysomnography

Participants slept in a standard hospital bed within a shielded video-PSG laboratory. A Somnoscreen 10-20 monitor (SOMNOmedics GmbH, Randersacker, Germany) using a standard PSG montage with electroencephalography electrodes (F3, F4, C3, C4, O1, O2, A1, A2 with a Cz reference, and 0.2–35 Hz filter), electro-oculography electrodes (placed 1 cm over/under the left/right lateral canthus), an infrared O_2 finger sensor, two chin EMG electrodes, a nasal airflow sensor and an oro-nasal thermistor were used. Apnea-hypopnea index was <5/h in all participants. Video and sound were recorded continuously (VID65A, HD resolution 2048 × 1536, SOMNOmedics). Polysomnograms were analyzed by a blinded, certified clinical neurophysiologist, according to standardized criteria [19] using Domino software version 2.5.0.

2.3.3. Melatonin

Food or drink was not allowed 30 min prior to each sampling. Five minutes before sampling, the mouth was rinsed with cold water. A piece of Parafilm® (Pechiney Plastic Packaging Company, Chicago, IL, USA) was chewed and two samples of ≥2 mL each were collected and placed in a refrigerator at 4 °C within 10 min. All samples were placed in a freezer at less than –20 °C immediately after midnight and analyzed with the Non-Extraction Melatonin Saliva enzyme-linked immunosorbent assay kit, supplied by IBL International GmbH (Hamburg, Germany).

A melatonin baseline was calculated as the mean value for samples taken at 20:00, 21:00 and 22:00. Normal (early) melatonin secretion onset was defined when a concentration either more than twice the baseline value, or baseline +2.5 standard deviations (SD), was measured either at 23:00 or at 00:00. This cut-off was modified from the 2 SD limit used by Chang et al. [20] in order to account for the observed baseline variability. Delayed dim light melatonin onset (DLMO) was presumed if concentrations had not reached one of the cut-off values at 00:00.

2.3.4. Sleep diary

Participants kept a graphic sleep diary of their subjective experience of sleep timing and duration for 14 days prior to the experimental night. A pencil was used to shade (or leave) 24 rectangular small boxes each representing 1 h of the day. Symbols were inserted for going to bed, lights off, and getting out of bed.

2.3.5. Sleep-related and psychiatric self-report questionnaires

Participants completed self-report questionnaires to assess circadian preference (Horne–Östberg Morningness Eveningness Questionnaire (MEQ) [21], and the Beck Depression Inventory (BDI) [22]).

2.3.6. Continuous performance test

In the present study, Conners' CPT II [23] was used to assess cognitive function. Letters A–Z were presented consecutively on a computer screen for 250 ms each in a pseudorandom fashion for 14 min. Inter-stimulus intervals varied between 1, 2 and 4 s. There were 324 targets (letters other than X) and 36 non-targets (the letter X). Participants were instructed to press a button as quickly as possible whenever a target was presented. Measures were: Hit-RT, mean reaction time for correct responses; commission errors, the number of failed withholdings to non-targets; and omission errors, the number of failed responses to targets.

2.4. Data analysis and statistics

The main variables were: CPT Hit-RT evening–morning difference; alarm clock level upon awakening; and sleep stage on awakening. Exploratory statistical data analysis was performed for the remaining variables.