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Original Article

Insomnia cycling with a 42-day infradian period: Evidence for two uncoupled circadian oscillators?

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ABSTRACT

Objective: To describe the unique case of a middle-aged woman with severe insomnia recurring with a regular infradian period without any other significant clinical condition. To infer the existence of a circadian dysfunction modeled according to the physical phenomenon of the "beats."
Patient/Methods: A two-year prospective observation by means of a sleep log was performed during the patient's normal life. She underwent one month of motor activity recording and also polysomnography, circadian rhythm of body core temperature and psychiatric evaluation during periods with and without insomnia.
Results: Visual inspection of the 293-day plot of the sleep log disclosed a regular 42-day rhythm of insomnia recurrence confirmed by a Discrete Fourier Transform. During the periods of insomnia, lasting 5–7 days, only moderate mood symptoms (depressive overlapping hypomaniac symptoms) were present. Treatment with sodium valproate was effective in curtailing insomnia.
Conclusion: The wax and wane infradian modulation of the sleep length suggested the presence of a basic mechanism similar to the physical phenomenon of the "beats," i.e., a long period modulation of the amplitude of an oscillating system due to the interference of two uncoupled oscillators with a slightly different oscillation frequency. Hypothesizing a dysfunction of the circadian component of sleep, namely two uncoupled circadian cycles, a simple mathematical model estimated the difference of their periods of oscillation |34 ± 2 min| and reproduced the sleep-log data of the drug-free period of observation.

1. Introduction

Complex behaviours may manifest with regular infradian periodicity both in healthy people and in patients with psychiatric disorders [1–4]. Menstrual migraine has, by definition, a monthly repetition, and cluster headache may recur with infradian regularity [5]. Some cyclic disorders have been described in the field of hematology, and cyclic neutropenia, the most studied, has a regular periodicity of 21 days [6].

Insomnia, the commonest sleep complaint and symptom of several neurological and psychiatric disorders, may display an infradian recurrence if driven by mood symptoms in a rapid-cycling bipolar disorder [7]. Insomnia cycling with regular infradian recurrence, however, has never been reported as a dominant complaint.

We describe the case of a middle-aged woman with a severe cyclic insomnia whose original points were (1) the regular infradian period of recurrence demonstrated upon extensive prospective clinical observation and neurophysiological monitoring, (2) the presence of moderate mood symptoms following the insomnia, (3) a good overall clinical response to treatment with sodium valproate. In this patient we hypothesized a dysfunction of the circadian component of sleep, which we modeled according to the physical phenomenon of the "beats," i.e., a long period modulation of the amplitude of an oscillating system as the result of two uncoupled oscillators cycling with slightly different frequency.

2. Case description

2.1. Subject

In June 2001, a 43-year-old woman with no history of neurological or psychiatric disorders came to the Sleep Center of the Depart-

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ment of Neurological Sciences, University of Bologna, Italy, complaining of "recurrent insomnia." She lives in a cottage in a small town of about 1500 inhabitants (429 meters of altitude, latitude 43.75, longitude 12.31) in a mountainous region of Central Italy. She had been in an orphanage from 2 to 14 years of age because of her family's economic difficulties, had a regular menstrual cycle since age 13, married at 17, had one daughter at 18 and held a middle school diploma. She worked as a waitress. She ate regularly, did not smoke or abuse alcohol or drugs. She defined her sleep (except for the "insomnia period;" see below) as "light but satisfactory and rest-giving;" she took afternoon naps of about 60 min two or three times a week.

2.2. Clinical features

The sleep disorder began when the patient was 36 years old, coinciding in the onset epoch with her husband's night shifts. From that time up to our observation – an interval of nine years – she experienced the following monthly features (we will call it the "insomnia period"). On a given night, she had difficulty falling asleep; after finally falling asleep, sleep was fragmented with a subjective restriction of total sleep time. In the following nights the disorder worsened with increasing sleep latency and a further restriction of total subjective sleep time. When awake in the night she lay in bed quietly and sometimes got up and to do her housework. This insomnia waxed to a maximum in 3–4 days, with 1 or 2 nights of total or nearly total subjective absence of sleep. A gradual recovery of subjective sleep occurred in the following 2–4 days. During the daytime in this "insomnia period" she usually felt a little depressed, anxious and tired, with a reduced ability to concentrate for the first two days; in the following 3–5 days she would report a slight elevation of mood, irritability, pressure of ideas and speech, distractibility, increased involvement in social and working activities, and moderate somatic symptoms (headache, musculoskeletal and abdominal pain, itch). Nevertheless, she was able to function normally in her family, social and working activities. Daytime naps seldom occurred during this "insomnia period," and there was no recovery of sleep during the day. Her relatives, directly interviewed, confirmed her clinical report. Neurological examination, EEG and brain MRI scan were normal.

3. Methods

3.1. Protocol of observation and intervention

A long prospective clinical observation (sleep log and psychiatric evaluation) of the patient during her normal life was devised. Neurophysiological observations (motor activity recording, polysomnography, circadian rhythm of body core temperature) were also planned to be performed during periods with and without insomnia of one single infradian cycle by means of brief recoveries in the sleep laboratory. The observation was organized in a first period without any pharmacological intervention (drug-free period) and a second period of prospective sleep log observation during the therapy with sodium valproate (therapy period).

3.2. Sleep log

The patient recorded the hours slept in a sleep log (30 min resolution) each morning on rising. Beginning at 12 a.m., sleep log results were plotted in 24-hour segments, each 24-hour segment displayed beneath the preceding one. By analogy with the procedure by Kim and Young [8] to verify if a homeostatic "sleep debt" was produced by the insomnia period, we arbitrarily compared the number of hours subjectively slept seven days before the nadir of insomnia (= night with fewest hour slept) with those slept seven days after the nadir. To reveal periodicities and the relative strengths of any periodic components, we performed a Discrete Fourier Transform of the daily recordings (hours slept in a day) for the period of observation when the patient was therapy free. This power spectrum gives a plot of the portion of the signal's power falling within given frequency bins.

3.3. Psychiatric evaluation

A standardized interview was carried out by a psychiatrist to yield demographic, socioeconomic and historical information. The patient's history was reviewed for psychotic episodes, suicide attempts, substance abuse, psychiatric or neurological illnesses and family psychiatric history. The Structured Clinical Interview for DSM-IV was used for evaluation. Personality disorders were evaluated using the Structured Interview for DSM-IV Personality. Psychopathological status was assessed using the Brief Psychiatric Rating Scale (BPRS) [9], the Young Mania Rating Scale (YMRS) [10], the Hamilton Depression Rating Scale (HAMDS) [11], and the Clinical Global Impression for Bipolar Disorder (CGI-BP) [12].

3.4. Motor activity recording

Spontaneous motor activity was measured by a wrist actigraph (Actigraph Mini Motionlogger, Ambulatory Monitoring Inc. Ardsley, NY, USA) worn on the non-dominant wrist. Data were collected in 60-second epochs in 24-hour periods. The collected data were analyzed by a computer program (Action 3, Ambulatory Monitoring Inc.). The mean (with standard deviation, SD) and median values of motor activity (movement counts per minute) were calculated. Beginning at 12 a.m., histograms of data were plotted in 24-hour segments and each 24-hour segment was displayed beneath the preceding one.

3.5. Polysomnography

The sleep–wake cycle was monitored by a portable dynamic polygraphic recorder (VITAPORT®) recording the electroencephalogram (EEG: C3-A2, CZ-A2, O2-A1), right and left electro-oculogram (EOG), electrocardiogram (ECG) and electromyogram (EMG) of the mylohyoideus and the right and left tibialis anterior muscles. The all night summary recording variables were derived from the visual scoring of recordings in 30-second epochs by an expert sleep technician blinded with respect to the sleep log data. Polygraphic data were analyzed according to standard criteria [13].

3.6. Circadian rhythm of body core temperature (BcT°)

BcT° was evaluated by monitoring rectal temperature every 2 min by means of a Mini–logger™ portable device. The analysis of rythmicity was performed evaluating the time series for BcT° according to the single cosinor method [14] using a computerized procedure [15]. This procedure determines whether or not there is a rhythm within a 24-hour period and evaluates the following parameters (and 95% confidence interval): (1) mesor (Midline Estimating Statistic of Rhythm): rhythm adjusted 24-hour average; (2) amplitude: the difference between the maximum value measured at the acrophase and the mesor in the cosine curve; (3) acrophase: lag between reference time (12 p.m.) and the time of highest value of the cosine function used to approximate the rhythm. The 24-hour pattern of BcT° was evaluated calculating the mean BcT° of each hour.