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Altered Sleep Rhythm: A Patient with a 10 to 15 Day Cycle

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Summary. A severely brain-damaged boy of 12 years had a prolonged sleep-wakefulness cycle of 10–15 days' duration. His body temperature followed a circadian rhythm, suggesting that some normal circadian oscillators were intact. The long sleep-wakefulness cycle could not be influenced by either methylphenidate administration or enforced wakefulness, which suggests that the cycle did not have the same properties as other rhythms, and the 10–15-day periods of sleep-wakefulness were probably controlled by mechanisms different from those operating in normal state. The case shows that there are multiple oscillating mechanisms in the control of different rhythms in humans.

Key words: Sleep disorder – EEG – Body temperature – Circadian rhythm

Zusammenfassung. Ein zwölf Jahre alter Junge, der seit seinem achten Monat an Enzephalopathie litt, zeigte einen verlängerten Schlaf-Wach-Zyklus mit einer Dauer von 10–15 Tagen. Seine Körpertemperatur folgte dabei einem circadianen Rhythmus, aus dem geschlossen werden kann, daß einige normale circadianen Oszillatoren intakt waren.

Dieser lange Schlaf-Wach-Zyklus konnte weder durch Gaben von Methylphenydat noch durch heftiges Wecken gestört werden, woraus man schließen kann, daß der Zyklus nicht dieselben Eigenschaften besitzt wie andere Rhythmen und die 10–15-tägige Periode des Schlafens und Wachens wahrscheinlich durch Mechanismen kontrolliert werden, die sich sehr von denen unterscheiden, welche das Verhalten im Normalzustand steuern.

Das Datenmaterial belegt das Vorhandensein multipler Schwingungsrhythmen beim Menschen.

Introduction

Recent studies on human chronobiology have shown that normal humans maintain activity-rest rhythms when isolated from all time cues. The period of such

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activity-rest rhythms have been reported (Aschoff et al. 1962; Chouvet et al. 1974) to be a non-24-h period, as many cases showed approximately 25 h, and in some subjects very long activity-rest periods of 30 to 50 h have been described (Chouvet et al. 1974; Mills et al. 1974; Weitzman et al. 1979). These observations were made in experimental environments such as cave, 'deep cellar', or controlled laboratories.

A 12-year-old boy with severe brain damage was found to have an unusually prolonged sleep-waking cycle. To our knowledge, this is the first case reported with such a long sleep-waking cycle in a normal 24-h day-and-night environment. In addition to polygraphic recording of sleep and waking, body temperature and blood cortisol were measured, which may provide us with some insight into the concept of multiple oscillators in humans.

Case Report

The boy was the oldest child of healthy and unrelated parents. Two younger siblings were healthy. He was born by normal delivery after 40 weeks gestation. The birth weight was 3450 g, the length 52.5 cm, the head circumference 35.0 cm. He appeared normal and fed well from the breast for the first 3 months. Head control was not satisfactory until 6 months of age. He barely recognized his mother after the age of 7 months. At the age of 8 months, while his mother held him in her arms, he suddenly stretched his legs and stiffened his arms for about 2 min, followed by a short period of sleep.

At the age of 11 months, he had a fever of 38–39°C and severe diarrhoea which lasted for several days. At this time, he suddenly developed tonic convulsions for about 20 min which were considered prolonged febrile seizures. Examination of cerebrospinal fluid (CSF) were unremarkable. The tonic convulsions were difficult to control. He was hospitalized for 1 year. After discharge, his mental and motor developments were retarded, but he had no convulsive seizures. He was admitted to our hospital at the age of 10 years.

Clinical Findings on Admission

He was 139 cm tall, weighed 22.8 kg with head circumference 48.5 cm. He did not seem to respond to external stimuli, but he perhaps recognized his mother and smiled. He was not able to stand and was usually bedridden. His developmental age was estimated to be between 3 and 7 months according to the Enjoji Developmental Test which is a modification of the Denver Developmental Screening Test (Frankenburg et al. 1967).

He appeared to have no visual problems and examination including visual evoked potentials was normal. Cranial nerve examination was normal and muscle tone was reduced. Blood and CSF examinations did not show any abnormal findings. Skull radiographs were normal but computed tomography showed a moderate dilatation of the lateral ventricles (Fig. 1).

After admission he developed physically (length 153 cm, weight 29.8 kg, and head circumference 51 cm) but did not show any motor and mental development.

Sleep-waking Rhythm

A few months after admission, nurses reported that he sometimes stayed awake day and night and sometimes slept the whole day. On inspection of his behaviour, there were distinct differences between the waking and the sleeping state. When he was awake his eyes were open, he appeared to look at something, he usually moved his hands and legs, sometimes he changed position on the bed, and made sounds. When he was asleep, his eyes were closed and he did not usually show much movement.

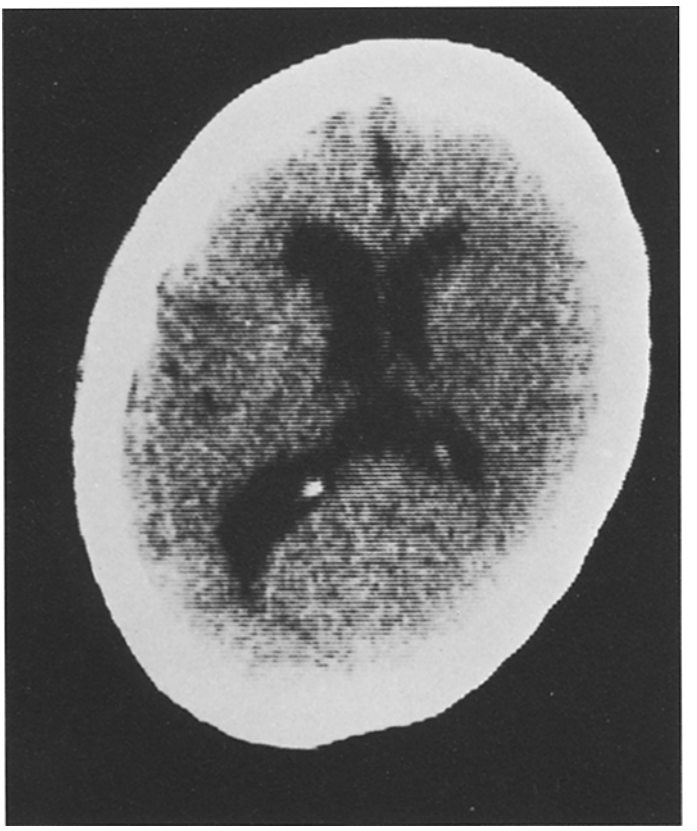

Fig. 1. CT scan showing moderate dilatation and asymmetry of ventricles

The patient's sleep-waking cycle was recorded continuously by inspection of his behaviour for more than 1 year. Repeated polygraphic recordings, usually extending from 24 to 48 h, were made to confirm the observations.

His characteristic sleep-waking cycle pattern was a prolonged wakefulness for 2–6 days followed by prolonged sleep for several days at a time (Fig. 2). This rhythm was repeated every 10–15 days for several months and then switched into an irregular sleep-waking cycle without any obvious change of the environment. Several months later the sleep-waking pattern returned spontaneously to the prolonged cycle. During the 7 years of observation, the development of this prolonged sleep-waking cycle was independent of seasonal changes.

Polygraphic Examinations

Polygraphic recordings usually extending from 24 to 48 h were made on several occasions. To retain as far as possible the patient's normal hospital routine, recordings were carried out at the bedside in the ward.

When the patient was awake, quite rhythmic theta activity appeared with frequent blinking artefacts (Fig. 3). While the patient was asleep, EEG showed three different stages: (1) Fast wave sleep in which rhythmic fast activity was predominant; (2) Slow wave sleep in which high voltage delta activity with some theta waves were observed; (3) REM sleep in which frequent eye

Fig. 2. Ten-day to two-week rhythm of sleep-waking for 4.5 months. Black line indicates sleeping periods with the 'double plot' technique. The abscissa is clock time

movements and decrease of muscle tone were recorded (Fig. 3). EEG did not show any sleep spindle, vertex sharp wave or K-complexes. Simulteneous observation of his behaviour and polygram confirmed the concurrence of EEG and behavioural sleep or waking state.

Body Temperature (BT)

BT was recorded with an indwelling thermistor in the rectum for 2–9 consecutive days including the polygraphic recording period. During prolonged period of both sleeping and wakefulness higher BT was shown in the afternoons (Fig. 4). Continuous recordings of BT for 9 days confirmed a circadian cycle of BT (Fig. 5). According to statistical analysis (ANOVA) of BT rhythmicity on the 9 consecutive days of data collection, there was circadian periodicity of 24.6 ± 4.1 h (mean $\pm$ SD) ($P < 0.01$). The peak BT value for a day was 37.3 ± 0.8°C and occurred at 5 p.m., and the minimum of 35.6 ± 1.1°C occurred at 5.20 a.m.

Cortisol Rhythm

Twenty-five microlitres of blood from the auricular lobe was sampled every hour throughout the polygraphic recording period using a calibrated micropipette. Blood cortisol was determined by the protein binding method of Murphy (1967) with a minor modification (Takahashi et al. 1979). Blood cortisol showed no obvious periodic changes. The mean blood cortisol level for 48 h was 4.1 ± 1.64 (mean $\pm$ SD) µg/100 ml.

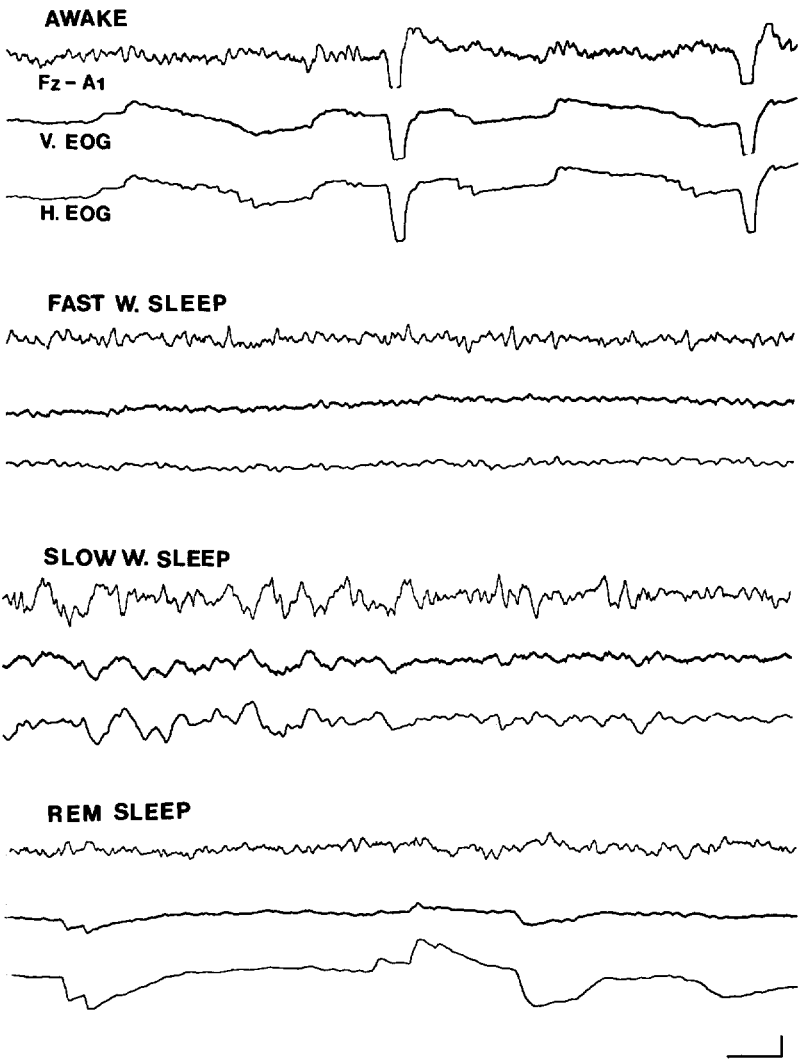

Fig. 3. EEG and vertical and horizontal EOGs during wakefulness and sleep (see in the text). Calibration mark indicates 50 μV/1 s

When the patient happened to have slept at night and stayed awake in the daytime, a normal circadian change of blood cortisol was observed.

In the ward, many problems arose because of the abnormal sleep-waking rhythm. For example, during a long period of sleeping, the boy was difficult to feed. On the other hand, he required more food during his long periods of wakefulness. Sometimes, he looked pale and uncomfortable during the long wakeful periods. Because of this, we tried to achieve a normal circadian cycle by interfering with the sleep-wake cycle by (1) manual awakening by shaking, making noises, local cooling, tactile stimuli, etc. from 8 a.m. to 6 p.m. for 2 weeks, (2) 7.5 mg methylphenidate at 7 a.m. for 2 weeks, or (3) administration of 5 mg methylphenidate at 5 a.m. for 2 weeks. The interval between the three treatments was more than 2 weeks which ensured that no effects of the former procedure remained. As shown in Fig. 6, forced awakening was not

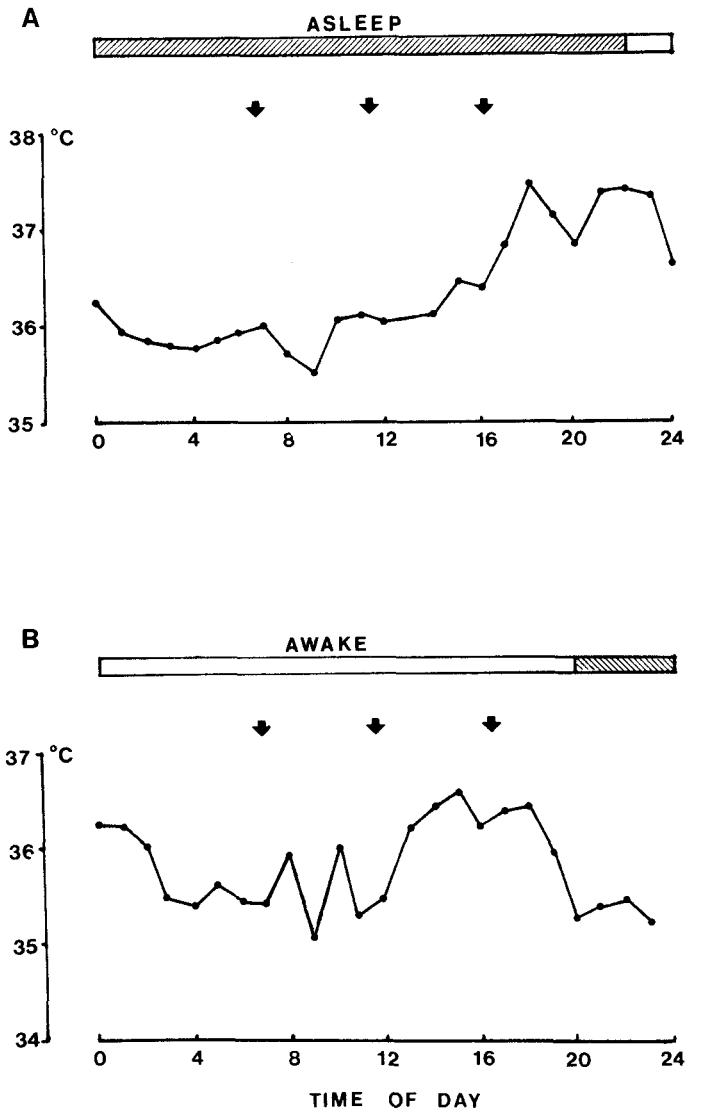

Fig. 4. Twenty-four-hour pattern of BT in 2 days. A: Patient slept whole day except for short waking period at midnight. B: Patient was awake most of the day. Arrows indicate the time of food intake

satisfactory, and administration of 7.5 mg methylphenidate resulted in the sleep onset and awakening time becoming very irregular every day in spite of fixed-time administration, while his total sleep time was reduced to 5.3 h/day compared to drug-free time (8.7 h/day). Administration of 7.5 mg was therefore considered not to be efficacious, and 5 mg was administered at 5 a.m. for 2 weeks. This dosage also resulted in irregular sleep onset and long sleeping period in daytime. These results suggest that methylphenidate was not effective in returning his abnormal sleep-waking cycle to 24-h rhythm. Immediately after each treatment, his sleep-waking cycle returned to the previous states.

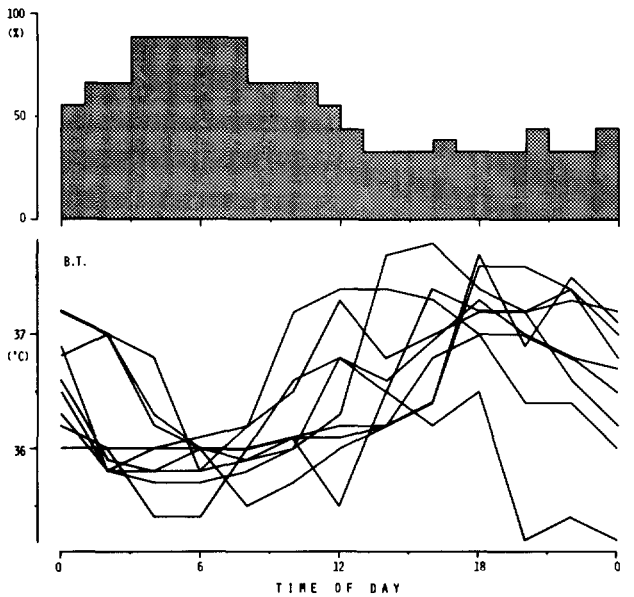

Fig. 5. Correlation between sleep-waking state and BT during 9 consecutive days. Dark area shows percentage of sleep in relation to clock time. Solid lines indicate BT

Discussion

A characteristic feature of the sleep-waking rhythm was a 10–15-day rhythm, which developed spontaneously and was not easily influenced by external stimuli. Sometimes this rhythm was unstable and became aperiodic without any obvious environmental change. His 10–15-day rhythm was considered to be an internal rhythm. However, BT developed rather stable circadian rhythm during both prolonged sleep-waking period and irregular sleep-waking period. Thus, BT rhythm seemed to be controlled by a different oscillator from that of the sleep-waking rhythm.

In experimental temporal and social isolation studies (Aschoff et al. 1967), human subjects showed free-running circadian rhythms of sleep-wakefulness and BT. Often free-running circadian rhythms of sleep-wakefulness, BT and other variables developed the same circadian periodicity of about 25 h. However, some subjects developed longer sleep-waking cycles (30–40 h), while about 25-h free-running BT cycles were maintained. This state was termed internal desynchronization. From these experiments, the hypothesis was derived that the human circadian system consists of multiple oscillators, which are usually coupled to each other but may change their phase relationship. The results of our study also support the multiple oscillator theory of human circadian rhythms.

These observations raise questions as to the localization of oscillators in humans. In rodents, the suprachiasmatic nucleus (SCN) appears to play an important role in the regulation of circadian rhythms (Ibuka et al. 1977). In a recent

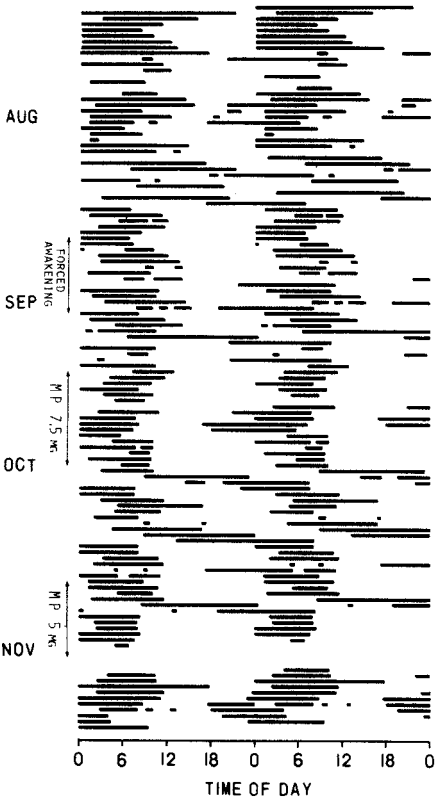

Fig. 6. Sleep-waking rhythms under the conditions of forced awakening and administrations of 7.5 mg and 5 mg methylphenidate (MP). (See Fig. 2 for explanation)

study of monkeys (Moore-Ede 1980) with SCN lesions, the circadian rhythm of BT remained although the circadian rhythm of rest-activity was completely eliminated. These results suggest that, in primates, BT is controlled by time-keeping systems other than SCN. In humans, however, very little is known about the localization of oscillators.

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