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Case report

Selective circadian rhythm disturbance in cerebral lymphoma

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Abstract

We present a patient with cerebral lymphoma who developed a selective circadian rhythm disturbance. Treatment with modafinil led to a considerable improvement in quality of life.

Keywords: Circadian rhythm; Sleep; Supra-chiasmatic nucleus; Hypothalamus; Non-Hodgkin's lymphoma; Modafinil; Quality of life

1. Introduction

There have been several case reports attributing sleep disorders to underlying cranial malignancy. Such disorders include hypersomnia [1–3], narcolepsy [4,5], insomnia [6], and obstructive sleep apnoea [7]. However, a selective circadian rhythm disturbance as a direct result of intracranial malignancy has not been described. We present a patient with primary cerebral B-cell non-Hodgkin's lymphoma who lost circadian control of sleep and temperature whilst retaining an intact homeostatic sleep mechanism.

2. Case description

A 39-year-old lady presented with hyperphagia, memory loss, intermittent confusion, and disinhibition. Ward staff noticed that her sleep pattern was erratic. She was often awake and eating at night. A magnetic resonance imaging (MRI) scan revealed a large right frontal lesion extending into the hypothalamus and basal ganglia, and a stereotactic biopsy found a mixed lymphocytic infiltrate, consistent with inflammation. As there was significant clinical improvement and resolution of the MRI appearances after 3 weeks of high dose dexamethasone, an acute encephalomyelitic illness was considered the most likely diagnosis.

Six weeks after stopping steroids, her condition deteriorated and she had two generalized epileptic seizures. The MRI changes had progressed; as well as involvement of the hypothalamus and basal ganglia, there was now nodular enhancement extending into both medial frontal lobes, the genu of the corpus callosum, the left internal capsule, and into the wall of the body of both lateral ventricles (Fig. 1). Following a further biopsy, a diagnosis of a high grade B-cell cerebral non-Hodgkin's lymphoma was made. After chemotherapy she underwent whole brain radiotherapy, receiving 45 Gy in 25 fractions, and was considered clinically to be in remission. She had a cognitive impairment particularly affecting memory and problem solving ability, hyperphagia sufficient to cause 40 kg weight gain, and an erratic sleep pattern.

She was referred to the sleep disturbance clinic 6 months later from palliative care, as her husband complained that her sleep pattern was significantly detrimental to their quality of life. He reported approximately four sleep episodes in every 24 h. After sleeping for approximately 1 h she would wake feeling refreshed, but 3–4 h later would fall asleep again, often after a meal. She slept longest at night. She experienced no jet lag while travelling to the Far East, and had ceased to dream.

She completed a sleep diary for 2 weeks and this showed that she slept for 8–12 h in every 24 h. This occurred in 3–6 episodes. She underwent 2-week actigraphic movement monitoring, which showed that she had 4–7 sleep episodes (mean 5.5) during each 24-h period. She slept for a mean of 6 h 20 min between 2100 and 0900 and for 3 h 25 min

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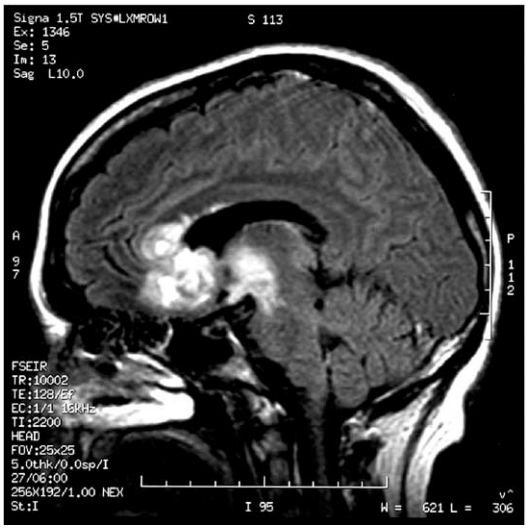

Fig. 1. MRI scan, sagittal section.

between 0900 and 2100 (Fig. 2). She underwent sleep and circadian rhythm studies (Figs. 3 and 4). Her tympanic temperature, instead of rising to a maximum during the afternoon and falling to a minimum at 0300–0500, showed four peaks during the 24 h, with sleep being initiated as her temperature fell. Four hourly urine samples were collected for melatonin and cortisol estimations. The total 24-h 6-sulphatoxymelatonin output was normal at 5.69 μg, but there was abnormally little difference between the day and night levels, and no discrete peak at night. Her cortisol level peaked between 1800 and 2200 (normal peak between 0700 and 0900). Polysomnography showed that the sleep architecture was normal within each sleep episode, although during the 24 h she had a slightly increased duration of stages 3 and 4 NREM sleep with a reduction in REM sleep.

She was commenced on melatonin 5 mg nocte. This had no effect on her sleep pattern, so modafinil was started, and increased to 300 mg at 0800 and 1500. This resulted in

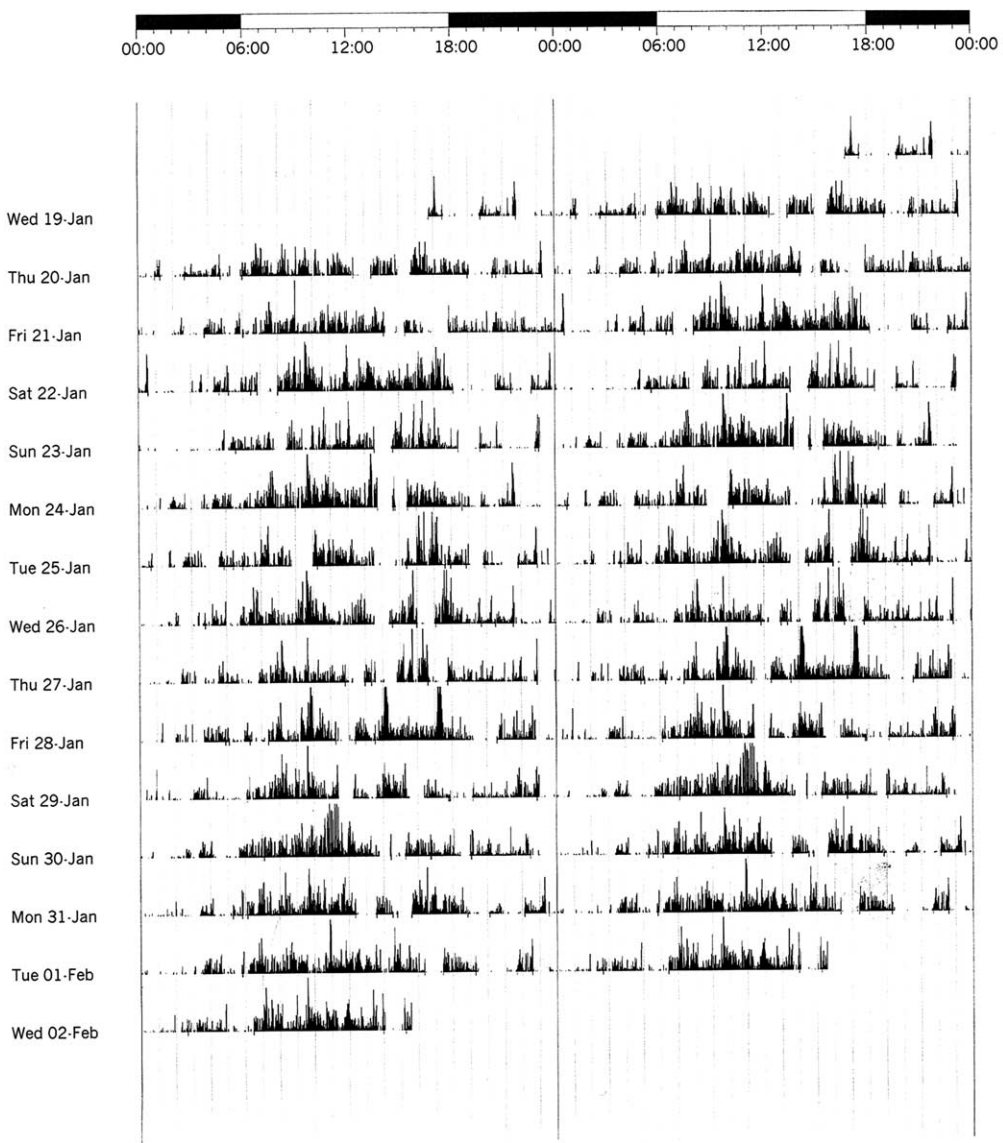

Fig. 2. Double plotted actigram (2 weeks).

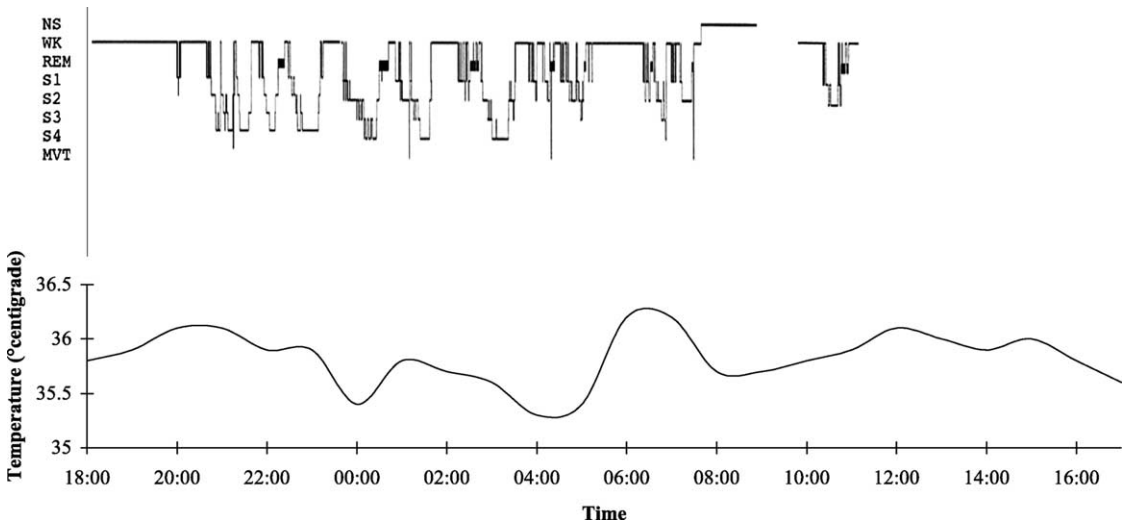

Fig. 3. Hypnogram and temperature record.

wakefulness from 0800 to 2300, followed by unbroken sleep from 2300 to 0600. As there was still some sleepiness after breakfast and in the afternoon, the doses were changed to 300 mg at 0600 and 400 mg at midday. The marked improvement in both daytime alertness and nocturnal sleep led to a significant increase in quality of life.

Four months later she developed a mild left hemiplegia. A computed tomography (CT) scan revealed recurrence of cerebral lymphoma. Her condition deteriorated steadily, and after a further 4 months she died. There was no autopsy.

3. Discussion

This patient's history and 2-week actigraphic movement monitoring confirmed that she had a polyphasic sleep pattern with approximately 5.5 sleep episodes in each 24 h, amounting to an irregular sleep–wake pattern. Polysomnographic monitoring did not reveal any significant physiological abnormality of her sleep, but her circadian rhythm studies showed a very unusual pattern. She had an abnormal diurnal pattern of temperature, but the onset of sleep coincided with a fall in body temperature, as in normal subjects, suggesting that the mechanisms linking sleep and temperature control within the central nervous system remained intact. There was no discrete melatonin peak during the night, but continual secretion throughout the day. The cause of this loss of circadian variation in melatonin secretion could be located at any site from the retino-hypothalamic tract to the supra-chiasmatic nuclei in the hypothalamus, which are the circadian rhythm controllers for the whole body, or along the efferent pathways from these nuclei to the pineal gland. The observation that the serum cortisol peak was around 12 h different to normal, taken together with the loss of the circadian rhythms of sleep and temperature, suggests that the most likely site of all of these abnormalities was in the supra-chiasmatic nuclei.

Loss of circadian control enabled the homeostatic drive to sleep, which increases with the length of time spent awake, to determine when sleep occurred. This was responsible for the polyphasic pattern that was observed. The longest sleep episode occurred at night when there was an absence of light and other external stimuli that might lead to wakefulness. Melatonin therapy was tried in order to synchronise the circadian rhythms, but the lack of effect suggests that damage to the circadian mechanisms was too extensive. Modafinil does not have any effect on circadian rhythms but does inhibit the hypothalamic ventro-lateral

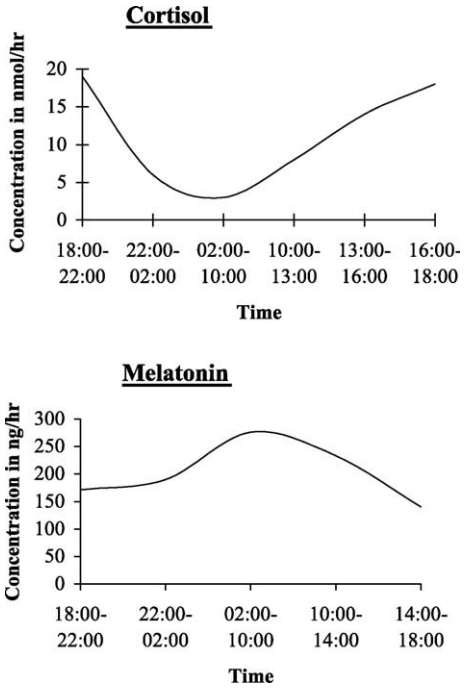

Fig. 4. Diurnal pattern of cortisol and melatonin levels.

pre-optic nucleus (VLPO), which itself inhibits both the histaminergic neurons in the tubero-mamillary nuclei, and promotes activity in the orexin releasing neurons in the lateral hypothalamus. Both of these wake promoting systems are therefore activated by modafinil. Our patient's improvement with this drug indicates that it was able to suppress the homeostatic drive to sleep sufficiently to enable her to remain awake continuously during the day.

These observations point to a selective damage by her cerebral lymphoma on the circadian rhythm controlling mechanism, probably in the supra-chiasmatic nuclei. The clinical features were present before radiotherapy or chemotherapy. Although an irregular sleep–wake pattern has been described as a consequence of diffuse non-malignant brain dysfunction such as in Alzheimer's disease [8,9], a selective circadian rhythm disturbance associated with an intact homeostatic sleep mechanism has not to our knowledge been described as a direct result of cerebral malignancy.

4. Conclusion

We report a case revealing a selective disturbance of circadian control of sleep, temperature and cortisol secretion, as a consequence of cerebral lymphoma. This case throws light on the circadian control of sleep, temperature and cortisol secretion and how this can be modified pharmacologically. Recognition of this problem is important, as treatment can considerably improve quality of life.

Acknowledgements

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