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A discrete lesion of ventral hypothalamus and optic chiasm that disturbed the daily temperature rhythm*

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Summary. A patient with a discrete metastasis in the ventral hypothalamus and optic chiasm is reported, who developed an abnormal daily rhythm of oral temperature without alteration of the 24-h mean temperature. This region, its afferents, and its efferents appear to be important in the neural regulation of human circadian rhythmicity.

Key words: Hypothalamic lesion – Circadian rhythmicity – Suprachiasmatic nucleus

Daily rhythms of biological processes are the overt manifestation of an innate timekeeping mechanism [1, 17] so that hormonal, temperature, sleep-wake and other rhythms are appropriately sequenced and integrated for concerted action. These rhythms are normally synchronized (entrained) to the 24-h day by periodic environmental time cues, especially the natural day-night cycle. Evidence from experimental animals now indicate that the suprachiasmatic nuclei (SCN) of the anterior hypothalamus are crucial components of the mammalian circadian timekeeping system [16].

Circadian rhythms have also been amply documented in humans [4], and anatomical [15, 20] and immunocytochemical [6, 23] techniques have been used in the identification of the human SCN. Disturbed rhythmicity may follow damage to the human hypothalamus [9, 12–14], but the responsible lesions have all been large and often poorly characterized.

Here we report a patient with a discrete metastasis in the ventral hypothalamus, optic chiasm, and neurohypophysis, providing a retrospective opportunity to determine the functional consequences of damage restricted to this site. We analyzed the daily rhythm of oral temperature because it is a well-characterized circadian rhythm [4] which had been measured and recorded in the patient's chart. Although temperature rhythms may differ in phase and amplitude in different individuals, the rhythm is remarkably consistent from day to day in a single subject [11]. Details and discussion of the clinical course have been reported elsewhere [3], but data for circadian rhythmicity were not presented.

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Case report

A 55-year-old postmenopausal woman was admitted on 22 June 1982. Ten days before admission she began drinking 10 l of ice water a day and urinating every 1 or 2 h. She had blurred vision in the peripheral right temporal field; this progressed centrally and involved the left temporal field 2 days before she was admitted. She slept more than usual at night.

In 1979 an adenocarcinoma of the rectum invading smooth muscle and lymphatic vessels with metastases to 2 of 30 mesenteric lymph nodes had been resected after radiotherapy. Carcinoembryonic antigen (CEA) was 2.3 ng/ml. She received no further treatment, and in the next 2 years the CEA ranged from 1.0 to 2.0 ng/ml.

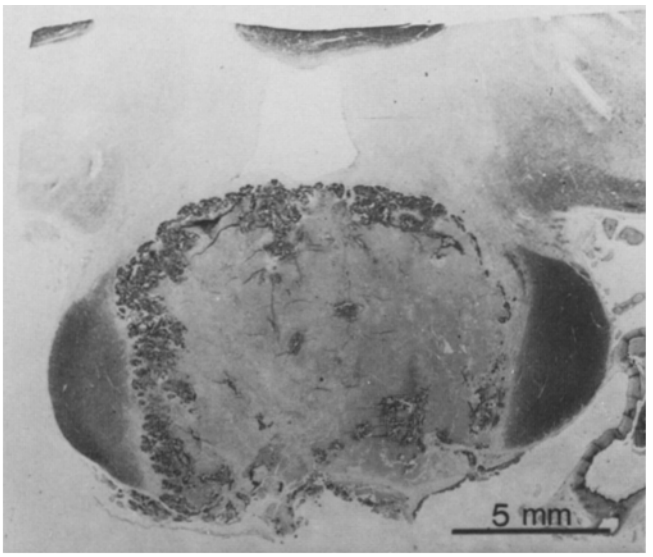
Examination on admission showed bitemporal hemianopia, worse in the inferior quadrants and on the right. Abnormal laboratory values included an erythrocyte sedimentation rate of 67 mm/h and a serum osmolality of 299 mosmol/l with a urinary specific gravity of 1.004. Morning cortisol and thyroid function tests gave normal results, but plasma luteinizing hormone (9 mIU/ml) and follicle-stimulating hormone (<2.5 mIU/ml) were low. A bone scan showed foci of increased uptake in the right fourth and ninth ribs and right acetabulum. CT showed a high absorption, irregular suprasellar mass; the sella turcica was normal in size and configuration. Cerebral angiogram revealed no aneurysm or tumor stain. At craniotomy on 25 June the mass was seen between the carotid artery and right optic nerve, expanding the infundibulum and infiltrating the hypothalamus. A biopsy showed adenocarcinoma. Radiotherapy was started on 8 July, and she was discharged on 10 July, taking intranasal desmopressin acetate, phenytoin (300 mg/day), and prednisone (45 mg/day).

In the next 3 weeks, she became blind in the right eye, dizzy, and hypophonic; she had difficulty swallowing both solids and liquids. Thyroxine was started as the free thyroxine index fell to 1.0 ng%, and prednisone was increased to 90 mg/day. She was readmitted on 30 July with bilateral partial basilar atelectasis, dehydration, and a serum osmolality of 318 mosmol/l. Examination showed her to be blind in all but the superior nasal quadrant of the left eye; the right pupil was unreactive to light. Thyroid function tests were normal. CEA was now 48 ng/ml. Osmolality was corrected to 294 mosmol/l, and she was treated with cefoxitin (6 g/day) and methyl-

prednisolone (40 mg every 6 h). Fluid balance was difficult to control, and she died on 29 August.

Autopsy findings

The brain weighed 1300 g. A granular white tumor involved the ventral hypothalamus, infundibulum, neurohypophysis, and optic chiasm about 3 mm behind the point at which the optic nerves entered the chiasm (Fig. 1). The mass had a 1.3 cm coronal diameter and extended 1.5 cm anteroposteriorly from the lamina terminalis to the anterior mamillary bodies. On microscopic examination, large basophilic cells ranged in an acinar pattern surrounded a necrotic, fibrinous center. The infundibulum, ventral hypothalamus, central optic chiasm and medial optic tracts were displaced and largely destroyed by tumor. Gliosis and marked neuronal loss extended superiorly to the ependymal cells lining the floor of the third ventricle, and in some areas the tumor eroded into the ventricle. Very few neurons were identifiable in the suprachiasmatic region (Fig. 2) in comparison with the corresponding region in normal brains. The supraoptic nuclei were gliotic and contained fewer neurons than normal, some of which had eosinophilic nuclei. The optic chiasm and tract fibers were vacuolated, with poor myelin staining. Other intracranial metastases were tiny and limited to the medial right occipital lobe, right cranial nerves V, VII, VIII, IX and X, left cranial nerves VII and VIII, and left flocculus. There were occasional microscopic collections of tumor cells in the subarachnoid space. Small metastases were also found in the thoracic vertebrae, fourth and ninth ribs, lungs, and liver.



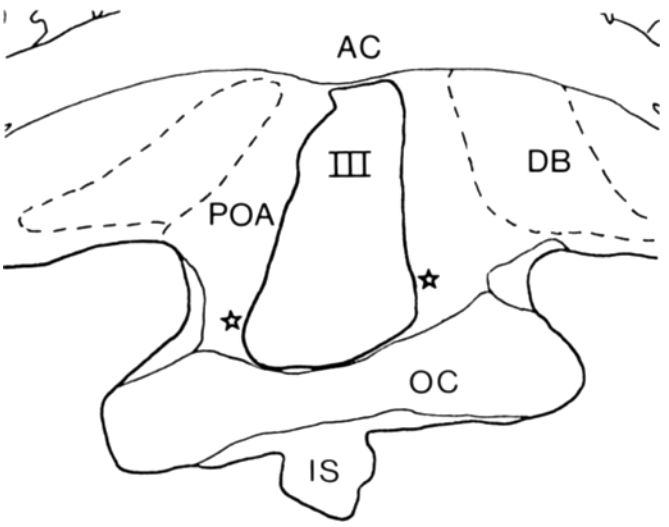


Fig. 1. *Top:* Coronal section through the metastatic adenocarcinoma at the level of the anterior hypothalamus (Luxol fast blue, hematoxylin and eosin). The central region of the optic chiasm and the ventral hypothalamus have been replaced by tumor (see text). *Bottom:* Line drawing [5] of the normal anatomy of the region. *Stars* represent the putative site for the suprachiasmatic nuclei; *AC* anterior commissure; *DB* nucleus of diagonal band of Broca; *IS* infundibular stalk; *OC* optic chiasm; *POA* preoptic area; *III* third ventricle

Temperature recordings

We charted the patient's oral temperature as recorded every 4 h from the initial 10 days of both the first (22 June–10 July) and second (30 July–29 August) hospitalizations. In the first admission the daily temperature rhythm was normal (peak at 2000 h) (Fig. 3A); the 24-h mean temperature was 98.3°F (36.8°C). In the second admission (Fig. 3B), the 24-h mean temperature was unchanged (98.2°F, 36.7°C), but daily rhythmicity was clearly disrupted. A two-factor analysis of variance with repeated measures on one factor showed a significant ($P < 0.05$ using the Greenhouse-Geisser procedure for conservative degrees of freedom [8]) interaction between admission (grouping factor) and time of day (repeated factor), indicating a change in the daily temperature profile from the first to the second admission.

Discussion

The discrete metastasis ultimately involved the ventral hypothalamus, optic chiasm, and neurohypophysis, causing rapidly progressive diabetes insipidus, gonadotropin deficiency, and visual loss. As the tumor enlarged between the first and second admissions, the daily rhythm of oral temperature changed without affecting the 24-h mean temperature. Although the sleep-wake cycle was also irregular, this could not be analyzed from the hospital chart.

We hypothesize that the location of this tumor was the most likely factor responsible for the disruption of temperature rhythmicity. Increased intracranial pressure from third ventricular tumors may abolish temperature rhythmicity [18], but there was no autopsy evidence of hydrocephalus. Administered steroids cannot account for the observed change in the daily temperature rhythm [19]. While it is possible that a tumor-induced sleep disturbance might have modified the rhythm, temperature rhythmicity is not a passive reflection of the daily rest-activity cycle [1, 17]. Temperature rhythms are generated independently; they persist despite continuous bed rest [26] or complete sleep deprivation [10], and temperature and activity rhythms may be dissociated by shifting sleep phase [22] or by isolating subjects from external time cues [2].

To our knowledge, this lesion is the smallest to be associated with a disturbed human circadian rhythm. Although the crucial aspect of the lesion could have been elimination of the

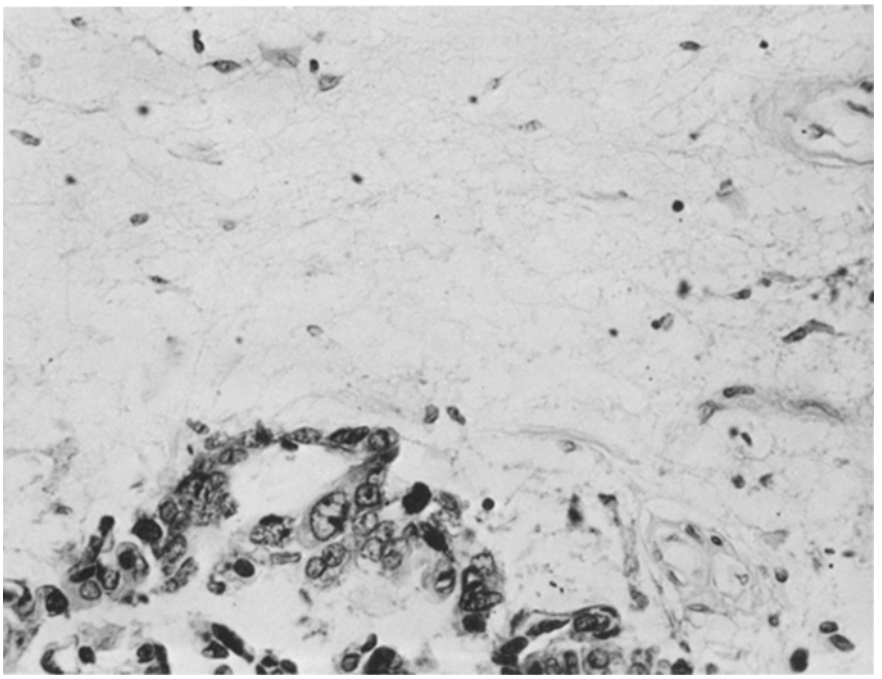


Fig. 2. Superior border of tumor and adjacent suprachiasmatic hypothalamus. Gliosis and virtually complete neuronal loss are evident. Cresyl violet, × 400

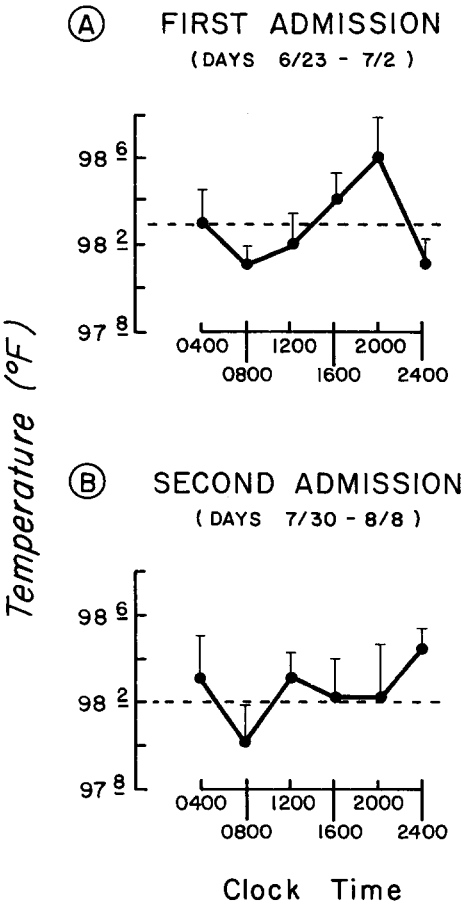


Fig. 3. Oral temperature (± SEM) as recorded every 4 h from the initial 10 days of both the first *(A)* and second *(B)* hospitalizations. *Dotted lines* represent mean oral temperature over the entire 24-h day. Since a complete set of measurements was not available for each day, the statistical analysis was carried out on five daily measurements with 4 days from each admission

SCN itself, experimental lesions of the nuclei in a nonhuman primate do not abolish temperature rhythmicity [7]. Therefore, destruction of retinal afferents to the SCN, disruption of efferents from the nuclei, or compromised function elsewhere in the ventral hypothalamus are more likely causes. Our serial (but discontinuous) temperature readings cannot differentiate true arrhythmicity from an abnormally expressed rhythm with distorted shape, modified phase, or altered periodicity.

Disorganized circadian function has been implicated in the pathophysiology of insomnia [25], affective illness [24], and aging [21]. Study of the anatomical components of the human circadian pacemaker will require prospective identification of patients for continuous recording of multiple physiological and hormonal measures.

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