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Case report

Melatonin and cortisol profiles in patients with pituitary tumors

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ABSTRACT

The optic tract section at the optic chiasm is expected to disturb the suprachiasmatic nucleus (SCN) rhythm, circadian rhythm and melatonin secretion rhythms in humans, although detailed studies have never been conducted. The aim of this paper was to describe melatonin and cortisol profiles in patients with a pituitary tumor exerting optic chiasm compression. Six patients with pituitary tumors of different size, four of whom had significant optic chiasm compression, were examined. In each brain, MRI, an ophthalmological examination including the vision field and laboratory tests were performed. Melatonin and cortisol concentrations were measured at 22:00 h, 02:00 h, 06:00 h, and 10:00 h in patients lying in a dark, isolated room.

One of the four cases with significant optic chiasm compression presented a flattened melatonin rhythm. The melatonin rhythm was also disturbed in one patient without optic chiasm compression. Larger tumors may play a role in the destruction of neurons connecting the retina with the suprachiasmatic nucleus (SCN) and breaking of basic way for inhibiting effect to the SCN from the retina.

1. Introduction

The day–night rhythm of Earth's rotation regulates light-dependent rhythms in living organisms [1]. The melatonin circadian rhythm is the most stable light-dependent rhythm in humans. Even after major surgery, it returns to its pattern in 24 h [2,3]. It has been estimated that melatonin secretion increases at night with a peak at 02:00 h and is low during the day [4]. It has also been proven that photic stimulation received through the retino-hypothalamic tract (RHT) stimulates the suprachiasmatic nucleus of the hypothalamus (SCN). The suprachiasmatic nucleus (SCN) plays a major role in generating the circadian rhythm in humans [5,6]. Recently,

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other important connections were described between the SCN and forebrain and midbrain structures, *inter alia* an intergeniculate leaflet regulating the SCN's activity [7,8]. Retinohypothalamic fibers synapse in the SCN and neuronal connections exist between the SCN and the intermediolateral gray column in the spinal cord. Preganglionic neurons pass from the spinal cord to the superior cervical ganglion, and postganglionic neurons project from this ganglion to the pineal in the nervi conarii [9,10]. The second most stable human rhythm is the cortisol circadian rhythm [11,12]. It is also related to SCN function, however, it is conducted *via* other connections from the SCN.

The aim of this study was to check how an obstruction of the connection between the retina and the pineal gland can disturb the melatonin circadian rhythm in humans. As an obstruction, pituitary gland tumors that were different in size and origin were analyzed. In the four cases considered in this study, optic chiasm compression which was significant but different in intensity was observed. In two cases no significant optic chiasm compression was stated. The cortisol circadian rhythm was used as a reference since it was expected that it would not be disturbed by pituitary tumors.

It was expected that in cases with significant optic chiasm compression, deviations would appear in the melatonin profile, namely, there would be a reduction in melatonin secretion at night (circadian rhythm 'flattening' at night) if the tumor were prompting nerve fibers innervating the pineal gland, or there would be hypersecretion of melatonin and/or the secretion peak shift if the retino-pineal connection were simply cut off by the tumor.

2. Materials and methods

Six patients were analyzed with pituitary tumors of different size and origin, two of these patients did not have optic chiasm compression detected in the Magnetic Resonance Imaging (MRI) examination and four of them had significant compression of the optic chiasm detected in the MRI (Table 1).

In each case a detailed interview regarding any other hormonal disturbances and concomitant disorders was collected. An MRI of the brain, the vision field, color vision field, a general ophthalmological examination and laboratory tests were also performed.

In all patients, medications were discontinued two days prior to hospital admission; all patients were awaiting the same surgical treatment. No history was reported of prolonged sleep–wake cycle disturbances caused by other reasons before admission, of prolonged use of drugs that could influence melatonin secretion, or of ocular comorbidities. After admission the patients were kept in a dark, isolated rooms for 12 h, from 22:00 to 10:00 and in a horizontal position for 13 h from 21:00 to 10:00 the next day. Melatonin and cortisol concentrations were measured at 22:00 h, 02:00 h, 06:00 h and 10:00 h. The melatonin ELISA kit was used to detect the melatonin level in the blood serum. The minimum detectable concentration of melatonin was 3 pg/ml. Intra-assay precision varied from 3.5% to 10.5%. Inter-assay precision varied from 9% to 19%. The plasma cortisol concentration was estimated by electrochemiluminescence immunoassay (ECLIA). The minimum detectable concentration of cortisol was 0.5 nmol/l. Intra-assay precision varied from 1.5% to 1.7%. Inter-assay precision varied from 1.8% to 2.8%. The acrophase, mesor, trough and bathyphase were determined for the rhythm analysis peak.

Because there was no control group, the patients' secretion curves were compared with data from the literature [13,14]. Secretion patterns in healthy individuals as described in the literature were compared with respect to age with the results of the patients in this study. Hormone peak concentrations in different points in time that were different from those in the references were interpreted as a disturbance in secretion.

All patients gave informed written consent according to the International Conference on Harmonization – Good Clinical Practice (ICH-GCP) guidelines (http://www.ich.org/LOB/media/MEDIA482.pdf). Ethical approval was obtained from the Bioethics Committee of the Poznan University of Medical Sciences.

3. Results

An abnormal melatonin rhythm was observed in two of six cases. The first case was a patient with pineal microadenoma

Table 1 – Patients characteristics.

Patient no and gender (man/woman)	1 woman	2 man	3 man	4 man	5 woman	6 woman
Age of patient	26	25	49	58	64	47
Length of tumor	0.9 cm	1.7 cm	2.5 cm	3.4 cm	3 cm	0.6 cm
Width of tumor	0.9 cm	1.6 cm	2.1 cm	3.4 cm	4 cm	0.4 cm
Altitude of tumor	0.9 cm	1.3 cm	3.4 cm	4.5 cm	5 cm	Not given
Volume of tumor	729 mm^3	3536 mm^3	17,850 mm^3	52,020 mm^3	60,000 mm^3	n/a
Pressure on the optic chiasm	No	Yes (mild)	Yes	Yes	Yes	No
Histopathological diagnosis	Micro adenoma	Rathke cleft cyst macroadenoma	Eosinophilic adenoma	Eosinophilic adenoma	Eosinophilic adenoma	Adenoma chromophobe microadenoma
Loss of field of vision	No	No	Yes (half of vision field)	Yes (half right eye – green color, full left eye)	Yes (concentric, red color)	No
Cortisol secretion	Correct	Correct	Correct	Disturbed	Disturbed	Disturbed
Melatonin secretion	Correct	Correct	Correct	Correct	Disturbed	Disturbed
Secretion	Prolactin	No	Prolactin	GH, prolactin	No	ACTH

with no evidence of optic chiasm compression. In this case hyperprolactinemia was found, but no interference with circadian melatonin and cortisol rhythms was observed, therefore, both rhythms in this patient were normal when compared to the age-matched pattern.

The second case was a patient with Rathke's cleft cyst macroadenoma with mild optic chiasm compression, which was detected in the MRI. Secretion disturbances of other hormones were not observed. Both of the analyzed rhythms in this patient were normal when compared to the age-matched pattern.

The third patient, with significant optic chiasm compression detected in the MRI and who exhibited a significant reduction in visual field during examination, had both rhythms at normal level. Hyperprolactinemia in this case did not disturb either of the analyzed circadian rhythms (Figs. 1 and 2).

The fourth patient displayed significant optic chiasm compression as detected in the MRI; here the visual field was reduced. Growth hormone (GH) and prolactin hypersecretion were present. The cortisol circadian rhythm curve was flattened with a significant lower cortisol serum level at the 6 a.m. check point (Fig. 4). The melatonin circadian rhythm was not changed in this patient when compared with the age-matched control (Fig. 3).

In the next two cases, both circadian rhythms were disturbed. The circadian rhythms' shapes were flattened, with reduced serum levels for both hormones at the 2 and 6 a.m. check points (Figs. 5–8).

In case no. 5 the tumor was large and in this patient significant optic chiasm compression was observed, which was confirmed in the MRI and during the visual field examination. In case no. 6 the tumor was small with no evidence of optic chiasm compression in the MRI examination; in this patient hypersecretion of ACTH was observed.

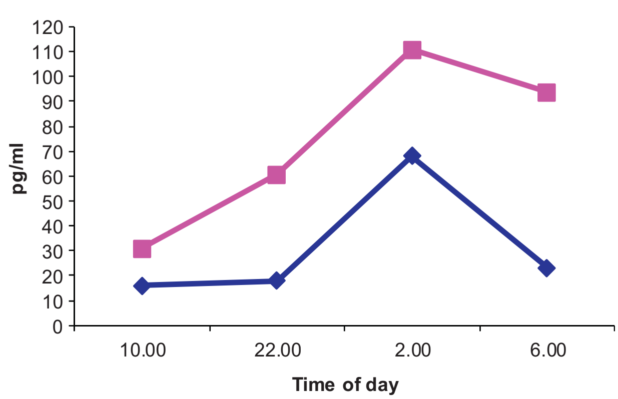

Fig. 1 – Melatonin profile in patent number 3; squares – patient's profile; diamonds – normal pattern corrected by age.

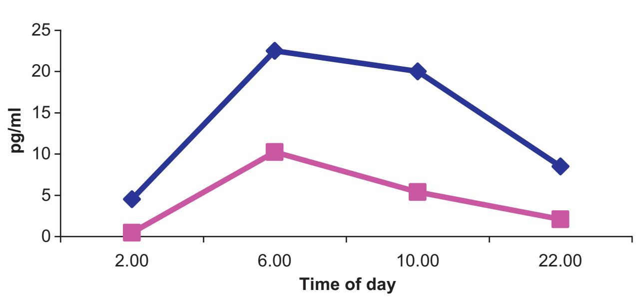

Fig. 2 – Cortisol profile in patent number 3; squares – patient's profile; diamonds – normal pattern corrected by age.

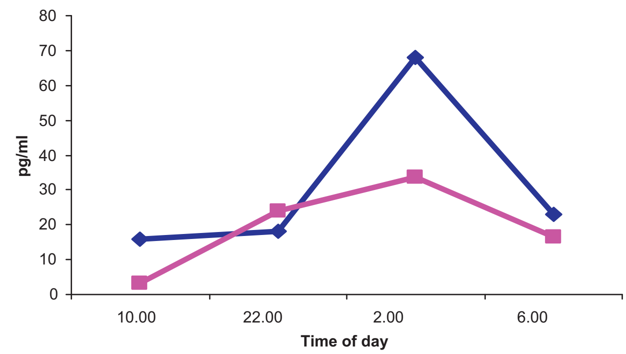

Fig. 3 – Melatonin profile in patent number 4; squares – patient's profile; diamonds – normal pattern corrected by age.

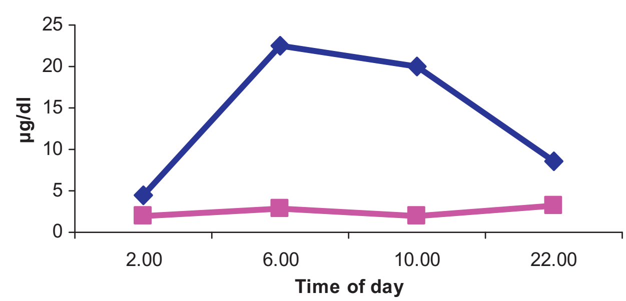

Fig. 4 – Cortisol profile in patent number 4; squares – patient's profile; diamonds – normal pattern corrected by age.

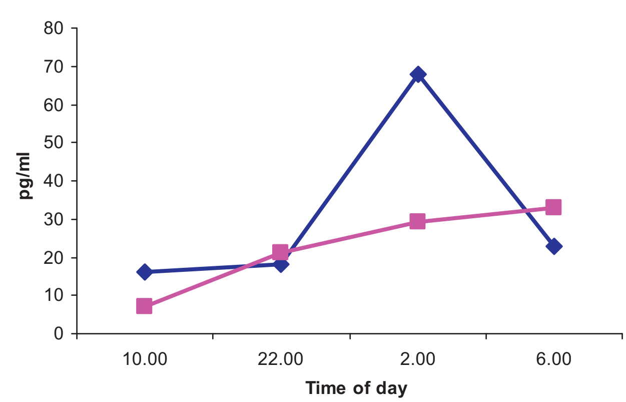

Fig. 5 – Melatonin profile in patent number 5; squares – patient's profile; diamonds – normal pattern corrected by age.

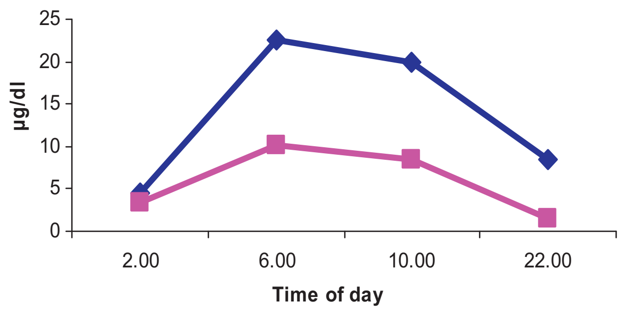

Fig. 6 – Cortisol profile in patent number 5; squares – patient's profile; diamonds – normal pattern corrected by age.

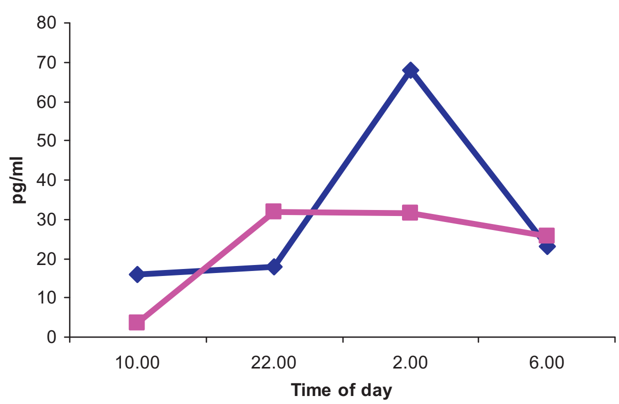

Fig. 7 – Melatonin profile in patent number 6; squares – patient's profile; diamonds – normal pattern corrected by age.

4. Discussion

As was expected, the melatonin rhythm was disturbed by a large pituitary tumor exerting significant pressure on the optic chiasm, as was observed in case no. 5, where the melatonin profile was 'flattened' with lower secretion at 02:00 h. This phenomenon suggests that in this case the tumor had stopped melatonin secretion at night acting as a light. However, in the two other cases, where milder but still significant compression

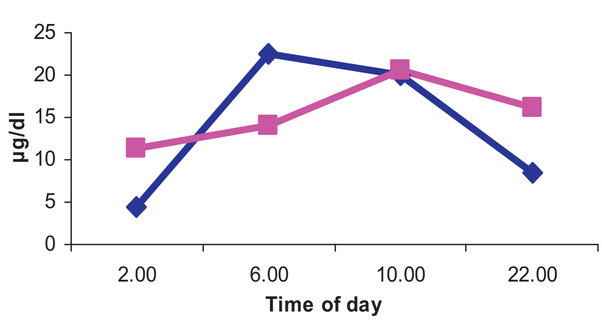

Fig. 8 – Cortisol profile in patent number 6; squares – patient's profile; diamonds – normal pattern corrected by age.

of the optic chiasm was detected (confirmed by MRI and the vision field examination), the melatonin secretion rhythm was not changed. This took place despite diagnosis of hypersecretion of GH in one case and hypersecretion of prolactin in the other.

The individual melatonin circadian rhythm is usually considered as very stable and affected only by large compression of the optic chiasm when evoked by a significantly large-sized tumor. It has been observed in animals that transection of the optic chiasm or the optic nerve abolishes the melatonin secretion rhythm and makes the nocturnal rise flatten [15,16]. Yet the question remains as to how optic chiasm compression alters the melatonin circadian rhythm, especially in its most significant night part? It was reported that disturbances in the circadian sleep rhythm negatively correlate with the melatonin concentration pointed four times a day in children with craniopharyngioma [17]. Optic chiasm compression disturbs the circadian rhythm of sleep and body temperature [18]. The melatonin rhythm was not considered with respect to optic chiasm compression. After removal of a tumor located in the neurophyseal region, melatonin rhythm disturbances were not observed, although information regarding the size and relation to the optic chiasm of these tumors was not provided [19]. Cut or destructive pressure acts as light strikes retina. Destruction of neurons connecting the retina with the SCN *via* an optic chiasm breaks a basic way for inhibiting effect contributed from a lit retina to SCN.

In patient number 6, both rhythms were disturbed when a small pituitary tumor secreting ACTH was diagnosed. Disturbance of the cortisol rhythm is easy to explain in this case but is not clear as regards melatonin. It has not been reported that ACTH hypersecretion disturbs the melatonin rhythm, thus the source of this phenomenon should be expected elsewhere.

Larger pituitary tumors can also cause disturbances in cortisol profiles, but the mechanism of this phenomenon is also unclear.

We also cannot confirm that prolactin disturbs melatonin or cortisol profiles, as was reported with respect to melatonin earlier [4]. The relationship between hypersecretion of the growth hormone (GH) and an altered circadian rhythm of cortisol secretion is possible, although no data are available in the literature. On the contrary, panhypopituitarism frequently results from two tumor conditions, *i.e.* craniopharyngioma or chromophobe tumors, which may compress the pituitary gland. One of the well-known effects of adult panhypopituitarism is decreased production of glucocorticoids by the adrenal glands.

Recently, a case of a GH-producing eosinophilic adenoma causing typical acromegalic features was described, with a concomitant lack of circadian rhythm of both ACTH and cortisol [20].

This is the first report to describe the impact of tumor-caused optic chiasm compression on melatonin secretion. Our findings confirm stability of the melatonin circadian rhythm in which only large tumors with a high optic chiasm destruction potential change circadian rhythm regulation in humans. The limitation of this study includes the short time period of the observation, *i.e.* one night. It is important to note that the conditions of the study were difficult for the patients, as they refused to stay in bed during the light phase.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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