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Case study

# Melatonin and cortisol secretion profile in patients with pineal cyst before and after pineal cyst resection

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ABSTRACT

A pineal cyst is a benign affection of the human pineal gland on the borderline between pathology and normality. Only a small percentage of patients present with symptoms and a surgical treatment is indicated in highly selected cases. A melatonin secretion in patients with a pineal cyst before and after a pineal cyst resection has not been studied yet and the effect of surgery on human metabolism is unknown. The present study examined melatonin, cortisol and blood glucose secretion profiles perioperatively in a surgical group of 4 patients. The control group was represented by 3 asymptomatic patients with a pineal cyst. For each patient, 24-h circadian secretion curves of melatonin, cortisol and glycemia were acquired. An analysis of melatonin profiles showed an expected diurnal pattern with the night peak in patients before the surgery and in the control group. In contrast, melatonin levels in patients after the surgery were at their minimum throughout the whole 24-h period. The cortisol secretion was substantially increased in patients after the surgery. Blood glucose sampling showed no statistically significant differences. Clinical results demonstrated statistically significant headache relief measured by Visual Analogue Scale in patients after the surgery. Despite the small number of examined patients, we can conclude that patients with a pineal cyst preserved the physiological secretion of the hormone melatonin while patients who underwent the pineal cyst resection experienced a loss of endogenous pineal melatonin production, which equated with pinealectomy. Surprisingly, cortisol secretion substantially increased in patients after the surgery.



## 1. Introduction

The pineal gland (epiphysis, corpus pineale) is a phylogenetically old brain structure present in almost every vertebrate. The physiological function of the pineal gland is closely connected with the regulation of circadian rhythms through its main hormone – melatonin (5-methoxy-*N*-acetyltryptamine).

A melatonin molecule is synthesized from tryptophan via a complex pathway, which is mainly regulated by an input from hypothalamic suprachiasmatic nuclei (SCN). The circadian rhythm, controlled by the SCN, is entrained to a light–dark cycle by photic information mediated by the retinohypothalamic tract [1]. A pathway linking the SCN to the pineal gland is multisynaptic and successively involves neurons of the paraventricular nucleus of the hypothalamus, sympathetic preganglionic neurons of the intermediolateral cell column of spinal cord and noradrenergic sympathetic neurons of superior cervical ganglion [1]. As a result of this complex neural signaling, melatonin secretion peaks during the subjective night in darkness and is minimal during the subjective day or in an illuminated environment [2,3]. A melatonin signal duration conveys information on the daylength, i.e. on a photoperiod into the organism. This physiological pattern enables inducing both, sleep/wake rhythm and seasonal rhythms (especially in animals [4]).

Effects of serum melatonin far exceed the biological rhythm regulation only. Melatonin regulates immunomodulation [5], maturation of hypothalamo-gonadal axis [6] and temperature homeostasis [4]. Several studies suggest that melatonin deficiency plays a certain role in the development of cardiovascular diseases [7–10], obesity [11], metabolic syndrome [12] and osteoporosis

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[13]. Some authors speculate that impaired melatonin secretion is connected to some psychiatric disorders such as schizophrenia, depression and anorexia nervosa [14–16]. It is, however, unknown whether this connection is a cause or a consequence, as these diseases strongly influence sleep per se. Melatonin supplementation showed some effect in treatment of sleeping disorders connected with jet-lag or shift work [17].

Interestingly, molecules of melatonin have been found in tissues other than the pineal gland, even in much higher concentrations [18]. This so-called extrapineal melatonin acts only as a local signaling molecule; it does not enter blood vessels and thus does not affect serum levels [19].

A pineal cyst (Fig. 1) is a benign affection of the pineal gland on the borderline between pathology and normality. The prevalence of pineal cysts in the general population reaches 1–2.4% [20–22]. They are to be found more frequently in women and their prevalence decreases with age [21,22]. Pineal cysts are often diagnosed incidentally on magnetic resonance imaging or computed tomography and are a relatively common reason for a neurological or neurosurgical consultation.

Only a small number of patients harboring a pineal cyst show any symptoms and only some of them need a surgical treatment. Obvious candidates for surgery are those patients with an obstructive hydrocephalus or a focal neurological deficit caused by a direct compression by a cyst (e.g. Parinaud's syndrome). Not a negligible percentage of patients present with non-specific complaints such as a headache, vertigo, syncope etc. It is controversial how to manage these patients with non-specific symptoms and different departments follow many different strategies [23]. For instance, in our department, we believe that surgery in these patients is a last resort treatment modality in refractory cases. Surgery might be considered after a meticulous clinical, endocrinological and neuropsychological examination that rule out other possible causes of symptoms.

The influence of pineal cyst on the physiological melatonin secretion profile is unknown. So far, it has not been studied whether a pineal cyst retains the capability of melatonin production or whether the production changes after a pineal cyst is removed.

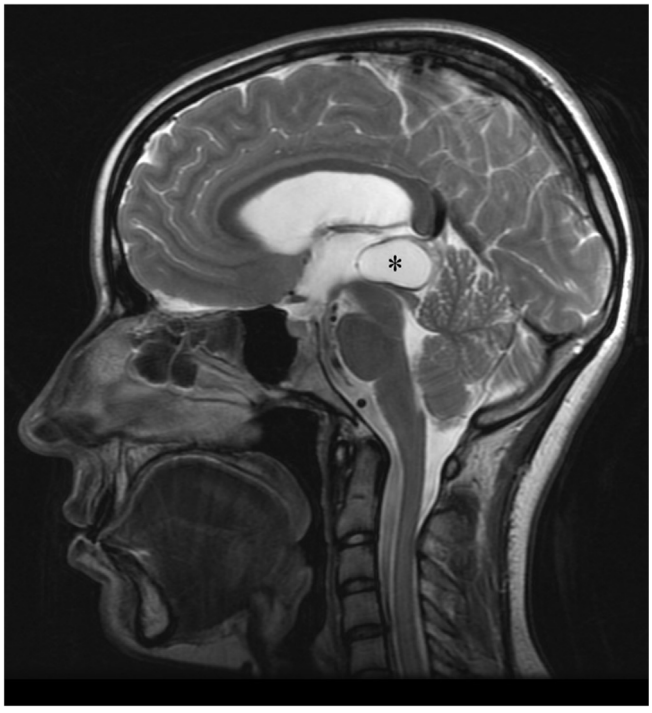

**Fig. 1.** Sagittal magnetic resonance imaging of the human brain (T-2 weighted image) showing a typical pineal cyst (asterisk).

This is the first pilot study of its kind that examines melatonin, cortisol and glucose serum levels in patients before and after the pineal cyst resection. If the pineal cyst resection proves to be associated with a complete absence of melatonin secretion (i.e. pinealectomy), it will be an important discovery with significant clinical implications. Such discovery would result in revision of indication criteria for the surgery and it would stimulate further research on clinical implications of melatonin deficiency.

## 2. Materials and methods

### 2.1. Patients

Four patients (three females, one male) scheduled for a pineal cyst resection were prospectively enrolled in the study in 2013. Presenting symptoms were a headache, vertigo, nausea and in one case monoparesis (see Table 1 for details). The control group was represented by three patients (two females, one male) who were diagnosed with a pineal cyst and a cyst resection was not indicated. Patients in the surgical group were labeled with arabic numerals, whereas patients in the control group with upper-case letters. Patient data are summarized comprehensively in Table 1.

The study protocol was identical for both, the surgical and control group. The surgical patients underwent this protocol twice, before and 6–10 days after the surgery during one hospital stay. The patients in the control group were examined during their 48-h hospital stay. The study protocol included melatonin, cortisol and glycemic circadian profile sampling, serum biochemistry test panel, questionnaires completion and clinical examination. The study was approved by Ethical Committee of Military University Hospital Prague and all patients signed an informed consent.

### 2.2. Surgery

During the surgical procedure (the pineal cyst resection), the patients were in a sitting position and a classical supracerebellar-infratentorial craniotomy was performed. Using an operational microscope, the pineal region was cautiously accessed. Special attention was given to the respecting bridging veins from the cerebellar surface towards the tentorium and thus preventing a cerebellar ischemia and swelling. A pineal cyst was meticulously mobilized from the surrounding structures and removed en bloc. Anesthesia and surgery duration was noted. A tissue specimen was examined by a senior neuropathologist.

### 2.3. Circadian profile sampling

Melatonin, cortisol and glycemic profile sampling protocols in patients before the surgery and in the control group were identical. A central venous catheter (CVC) was used for the blood sample collection. We investigated the possibility of less invasive way of the sample collection – a peripheral venous catheter, which showed to be an insufficient venous access for frequent blood sampling.

On the admission day, a clinical examination was performed and CVC inserted. In order to avoid sleep disturbance, patients were placed in single rooms. The first night was intended for a hospital environment adaptation. The first venous blood sample was collected on the second day at 05:00 and repeated every two hours since then until 05:00 on the day 3 (i.e. 13 samples in total during 24 h). Light in the patient room was turned off at 22:00 and turned on at 06:00 and the patient was woken up. A meal was provided at fixed hours: 8:00, 12:00, 18:00. During the night, blood samples were taken using a small pocket-sized flashlight with a red filter.