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# A rare case of pineal cyst and epilepsy with high salivary melatonin concentration

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Little is known about the incidence and symptoms of pineal cysts in children. It has been observed that they present with disturbances of melatonin secretion. The latter is known to have anti-convulsant properties, but pro-convulsant effects have been described as well. We present a rare case of pineal cyst combined with the partial epilepsy with secondary generalization. The aim of the analysis of the present case history was to zoom into the relationship between epilepsy, changed sleep pattern and altered concentration of melatonin. We compared diurnal melatonin secretion in the present case to the values of the group of 10 comparison children. Saliva melatonin concentrations were collected during 24 hour period, at every 3 hours and measured using the immunoassay method. Melatonin concentration in the presence of pineal cyst was four times higher and peaked earlier, as compared to the values of the control group. The role of endogenous melatonin in epilepsy remains controversial, but analysis of melatonin secretion may be helpful for the diagnosis and prognosis of the pineal cyst and selection of treatment strategy.

**Key words:** pineal cyst, melatonin, epilepsy

## INTRODUCTION

Pineal parenchymal tumors are rare. They account for 0.3% of primary brain tumors (1) and based on cellular structure can be further subdivided into pineocytomas (45%), pineoblastomas (45%) and pineal parenchymal tumors with intermediate differentiation (10%) (2). Pineoblastomas have a lower incidence of cystic change, and large cysts are less frequent in these tumors than in pineocytomas (2).

The pineal gland is secreting the hormone melatonin (MLT); it was identified in 1958 by Lerner et al. (3). The MLT secretion is controlled by a multisynaptic pathway which originates in the suprachiasmatic nucleus of the hypothalamus and is modulated by the noradrenergic system. The diurnal rhythm of MLT is light-dependent. MLT secretion peaks between 2 a.m. to 4 a.m., and its level is low or unmeasurable during the light period of the day (4). Melatonin itself influences a number of rhythmic physiological activities common for all mammalian species, such as seasonal reproduction, circadian thermoregulation (5).

Recent research on melatonin has provided evidence that this hormone may play an important role in epileptogenesis. Initial experimental animal studies have shown that MLT has anticonvulsive properties (6, 7, 8), however it has been observed that MLT may increase epileptic activity in the hippocampus and potentiate seizures (9, 10, 11). Thus, experimental data on MLT effect on epilepsy is so far inconclusive. Human studies have demonstrated that MLT has effect on brain electrical activity (12). In addition, a number of clinical studies have shown that administration of melatonin has reduced the frequency of seizures and improved sleep (13, 14). In contrast, elimination of melatonin after pinealectomy may cause sleep disturbances, such as late afternoon sleep, or even induce seizures (15, 16).

Little is known about the incidence and symptoms of pineal cysts in children. A single case of infantile spasms in a patient with multiple pineal cysts has been reported (17). A study by Mandera et al. (18) has shown increased serum melatonin concentrations at night in two children with pineocytomas before surgery. None of them had epileptic seizures. Thus, relationship between alterations in melatonin secretion due to pineal tumours and seizures is not established.

We report a rare case of pineal cyst with disturbed MLT secretion in a 10-year old boy who presented with a short history of sleep disturbances followed by the onset of nocturnal epileptic seizures.

## SUBJECTS AND METHODS

A ten–year old boy with pineal cyst and epilepsy and 10 comparison children (mean 14.2 ± 1.9 yrs) participated in the study. Children were recruited from the Department of Child Neurology, Vilnius University Children's Hospital. Children of comparison group were chosen from children who had cephalgia, but no severe neurological disorder, no sleep disorders. Four children were recruited from the families of colleagues and acquaintances. The study was approved by the Bioethics Committee of Lithuania.

### Clinical investigations

The 10 - year old boy, P.B., was born at term, from uneventful pregnancy, had normal developmental milestones. Two months before the seizure episode he presented with a change in the sleep pattern: awakening during the night, early morning wake-ups, 5-6 am. The first episode of repetitive seizures occurred at 9.5 yrs of age, during sleep, at 22 pm and 23 pm. Neurological and somatic investigations revealed no changes. Sexual maturity of the boy was within age limits. No changes were seen on fundoscopic examination. Routine daytime electroencephalography (EEG) showed normal background activity with local slowing and sharp waves temporo-parietooccipitally, on the left side, with short 3s duration episodes of generalized activity. Magnetic resonance imaging (MRI) investigation revealed a cyst of pineal gland, with a homogeneous structure and sharp clear boundaries. In addition, the circadian rhythm of daily body temperature was measured every 3 hours daily.

Follow-up at 6 months after admission to our hospital showed that he was continuing antiepileptic treatment with oxcarbazepin and was seizure–free, but epileptic changes recorded by EEG persisted, together with sleep disturbances, i.e. awakening during night, sleep hyperhydrosis, teeth grinding (19).

### Laboratory measurements of MLT

Measurements of melatonin in children were performed after three days of admission to the hospital. The saliva samples of all children were collected in 2005, from January to May (day length 7 hr 30 min to 16 hr 16 min). Artificial light in the ward was measured with a JU-116 luxmeter. Saliva melatonin concentrations were collected during a 24–hour period every 3 hours. Immunoassay, ELISA kits (Bühlmann Laboratories AG, Switzerland) were used for the MLT measurements.

## RESULTS AND DISCUSSION

We presented the case of a child with symptomatic partial epilepsy with secondary generalization, the cause of which may be related to the pineal cyst (Fig.1). Interestingly, he had a remarkably increased night secretion of MLT. His peak saliva concentration was 162 pg/ml, i.e. four times higher than the mean values at the same hour found for the age group, 34.5 ± 10.9 pg/ml (mean ± SEM) (Fig. 2).

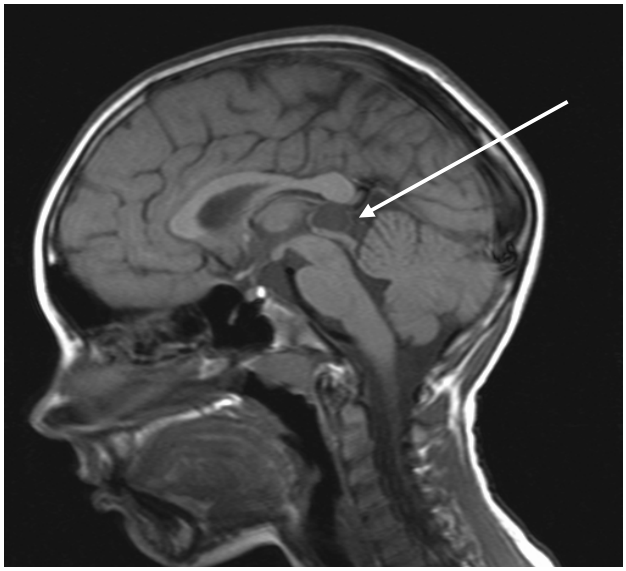

**Fig. 1.** MRI of subject P.B., showing a cyst of the pineal gland

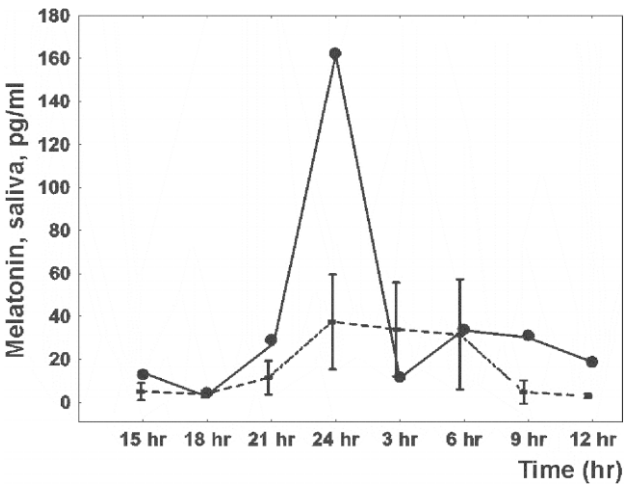


**Fig. 2.** Melatonin secretion profile of subject P.B., showing a high and early peak of melatonin secretion (concentration in saliva) (solid line) as contrasted to the mean melatonin secretion of comparison group (dashed line). Vertical bars denote 0.95 CI

It was in parallel with decreasing nocturnal temperature drop (Fig. 3). In addition, the maximum MLT concentration occurred earlier, at the onset of sleeping hours, and was low in the early morning hours. The decreased nocturnal melatonin concentration has been related to the altered sleep mechanisms (20). Thus, early fall in MLT secretion levels may explain the early awakening pattern in the present case. The body temperature of this child was consistently significantly lower as compared to the body temperature fluctuations of the comparison group (Fig. 3), suggesting a more generalized disturbance of circadian rhythms.

Of notice in this case is also the onset of seizures at 22–23 pm. We cannot exclude that a high MLT concentration occurred just after the epileptic activity period and might be related to the post-ictal phenomena. This phenomenon has been recently described by Bazil

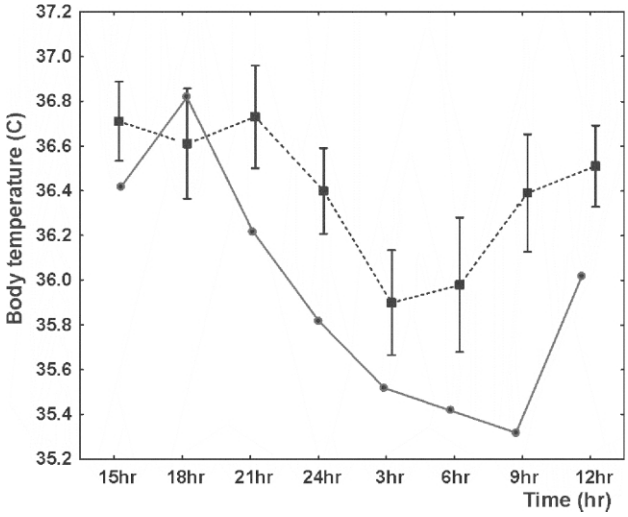


**Fig. 3.** Body temperature of subject P.B., showing significantly lower decrease in night temperature (solid line) as compared to the mean fluctuations of body temperature in the control group of children (dashed line). Vertical bars denote 0.95 CI

et al., (21) in a group of children with severe temporal epilepsy, who had a low MLT salivary concentration at baseline, but increased MLT levels after seizures. A possible relationship with post-ictal sleepiness has been suggested.

The combination of pineal cyst and seizures is very rare. The clinical profile of the present case differs from the cohort of children with pineal gland pathology presented by Mandera et al. (18). Very high night levels of serum melatonin have been found in two patients with pineocytomas, but not in children with benign pineal cysts. None of the children with pineal cysts have developed epileptic seizures. The authors have suggested that changes in melatonin concentration may be rather indicative of neoplastic lesions in the pineal gland.

Yet another explanation of high MLT saliva concentrations may be related to the use of anti-convulsant medication. The effect of anticonvulsants on MLT secretion and excretion pattern, to our knowledge, has not been described. It may be of interest for the future studies, when evaluating add-on effects of melatonin therapy in patients with combined seizures and sleep disturbances. It has been suggested that melatonin can serve as add-on therapy in children with epilepsy, especially if night seizures are predominant and combined with sleep disturbances (13). The present case, however, suggests that MLT administration in seizures has to be approached with caution, and MLT concentrations should be investigated if add-on therapy with melatonin is planned.

## CONCLUSIONS

The present case presents the clinical situation when the pineal cyst and subsequent increase in melatonin secretion may have influenced the onset of seizures. This case elucidates the controversy in the understanding of the role of endogenous melatonin in epilepsy. The presumed mechanism is that a decreased endogenous level of melatonin may lead to the sub-activation of melatonin receptors in the hypothalamus, suprachiasmatic nucleus and may result in the lack of anticonvulsant MLT activity and, thus, disinhibition of epileptic activity. If so, administration of exogenic melatonin could be beneficial add-on therapy in the treatment of seizures. However, the present case indicates that this relationship needs to be studied extensively before such recommendations can be advocated.

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## KANKORĖŽINĖS LIAUKOS CISTOS IR EPILEPSIJOS SU PADIDĖJUSIA MELATONINO KONCENTRACIJA SEILĖSE RETAS KLINIKINIS ATVEJIS

Santrauka

Vaikų kankorėžinės liaukos cistų simptomai nėra pakankamai ištyrinėti. Sunki ir ankstyva jų diagnostika, nes nėra aiškių klinikinių požymių. Ši liauka išskiria hormoną melatoniną, kurio reikšmė epileptogenezėje pastaruoju metu vis daugiau tyrinėjama. Pirmieji eksperimentiniai tyrimai su gyvūnais bei klinikiniai tyrimai skiriant egzogeninį melatoniną, kaip papildomą vaistą traukuliams gydyti, patvirtina prieštraukulinį melatonino poveikį. Tačiau kelių mokslinių darbų rezultatai leidžia įtarti ir prokonvulsinį melatonino veikimą.

Mes aprašėme 10 metų berniuką, ištirtą po pirmojo epilepsijos priepuolių epizodo. Diagnozavę pacientui kankorėžinės liaukos cistą, imunofermentiniu (ELISA) metodu ištyrėme melatonino kiekį jo seilėse. Duomenis palyginome su dešimties tuo pačiu metu tirtų kontrolinių vaikų tyrimų vidurkiu. Nustatėme, kad melatonino koncentracija yra ženkliai didesnė nei kontrolinių vaikų. Melatonino reikšmė epileptogenezėje, taip pat diagnozuojant kankorėžinės liaukos auglius yra diskutuotina ir reikalauja išsamesnių studijų.