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Original Article

Evaluation of Plasma Melatonin Levels in Children With Afebrile and Febrile Seizures

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ABSTRACT

BACKGROUND: Melatonin modulates central nervous system neuronal activity. We compared the melatonin levels of patients with febrile and afebrile seizures during and after seizure with those of healthy controls. **METHODS:** We enrolled 59 individuals with afebrile and febrile seizures (mean age, 6.09 ± 4.46 years) and 28 age-, sex-, and weight-matched healthy children. Melatonin levels were measured near the time of a seizure (0 to 1 hour) and at 12 and 24 hours post-seizure, and control melatonin levels were measured from a single venous blood sample. **RESULTS:** Plasma melatonin levels increased during seizures in the study group ($P < 0.001$). Post-seizure plasma melatonin levels were significantly lower in the study group than in the control group ($P < 0.05$). Plasma melatonin levels did not differ between patients with afebrile seizures who had and had not used antiepileptic drugs. Daytime (8 AM to 8 PM) and nighttime (8 PM to 8 AM) post-seizure melatonin levels were not significantly different. **CONCLUSIONS:** Melatonin levels were lower in pediatric patients prone to seizures than in healthy children and increased during seizures. Further research is needed to test the role of melatonin in the pathophysiology and treatment of epilepsy.

Keywords: antiepileptic, epilepsy, febrile seizure, melatonin

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Introduction

Epilepsy is the most common chronic childhood neurological condition, with an estimated prevalence of 0.5%-1%.[1] In contrast, febrile seizures typically occur in otherwise normal children between ages one month and five years of age.[1] Febrile seizures have a prevalence of 2% to 5% and are the most common type of seizure in children.[2,3]

Excitatory neurotransmitters such as glutamate and aspartate are believed to underlie the initiation and spread of epileptic attacks in the mammalian brain.[4] This hypothesis is supported by evidence showing that inhibitory neurotransmitters, such as glycine and gamma amino butyric acid (GABA), prevent epileptic attacks by hyperpolarizing cell membranes.[5] Moreover, nitric oxide (NO) may act as a proconvulsant or anticonvulsant depending on the dose,[6] and a decrease in NO levels has an anticonvulsant effect.[7]

The importance of the pineal gland and pineal indoleamines for the regulation and stabilization of electrical activity in the central nervous system is well established.[8] The pineal gland is a neuroendocrine organ that synthesizes and secretes melatonin in a circadian pattern such that plasma levels are low during the day and high at night.[9]

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Melatonin has anticonvulsant, sedative, and hypnotic effects in mammals.[10-13] This hormone suppresses neuronal excitation by inhibiting glutamate[14-17] and neuronal nitric oxide synthase activity and decreasing NO production[18,19] via increased cell membrane permeability of chlorine through Gamma-Aminobutyric Acid a (GABAa)–chloride channels.[20,21]

We investigated the relationship between a possible anticonvulsant effect and plasma levels of melatonin. Therefore, we measured melatonin levels in patients with afebrile and febrile seizures during and after seizures and compared them with melatonin levels in a healthy control group.

Materials and Methods

Participants

A total of 59 patients with seizures (29 afebrile and 30 febrile) from the Department of Pediatrics, Gülhane Medical Faculty were enrolled in the study. None of the patients with febrile seizures had a history of antiepileptic treatment. Of the patients with afebrile seizure, 11 had received antiepileptic medication; the remaining 18 presented with their first afebrile seizure and had received no previous antiepileptic treatment. We divided the patients according to whether their seizure occurred during the day (8 AM to 8 PM) or night (8 PM to 8 AM). The control group consisted of 28 age- and sex-matched healthy children.

We obtained information concerning age, sex, and weight from all participants in addition to their medical records, along with information about antiepileptic medication usage, additional systemic diseases, and family history. Patients who reported regular use of certain medications and experienced seizures caused by intracranial hemorrhage, electrolyte imbalance, or a systemic disease were excluded from the study. This study was conducted according to the principles expressed in the Declaration of Helsinki, and ethical approval was obtained from the Gülhane Medical Faculty ethics committee. Written informed consent was obtained from all participants and their families.

Sample collection and measurement

We measured melatonin levels in venous blood samples obtained from patients during the first hour and at 12 and 24 hours following seizures. The melatonin levels of the control group were measured from a single venous blood sample obtained between noon and 2 PM. The samples were centrifuged for 5 minutes at 3500 rpm, and the serum and plasma were aliquoted, labeled, and maintained at −80°C until analysis.

Plasma melatonin levels were measured in the Gülhane Medical Faculty Department of Medical Biochemistry High Performance Liquid Chromatography (HPLC) Laboratory using an Agilent 1200 HPLC system (Agilent Technologies, Santa Clara, CA). We used Phenomenex Inertsil C18 HPLC columns, 5 μ particle diameter, 150 × 4.6 mm dimensions (Phenomenex, Torrance, CA), and an ODS-2 reversed phase column with a mobile phase consisting of sodium acetate/acetonitrile (75 mM sodium acetate/acetonitrile [72:28, v/v; pH: 5]).

Statistical analysis

The distribution characteristics of the variables were taken into account for the between-group comparisons. The Wilcoxon test was used to assess non-normally distributed dependent variables, and the Kruskal-Wallis or Mann-Whitney *U* tests were used for the independent variables. Pearson correlation test was used to assess intervariable correlations. *P* values <0.05 were deemed to indicate statistical significance.

Results

Patient characteristics

We enrolled 59 patients (31 males and 28 females) with a mean age of 6.09 years (range, 8-16 years). The healthy control group comprised 16 males and 12 females with a mean age of 7.27 years (range, 1-16 years). The control and study groups were age and weight matched (Table 1).

Plasma melatonin levels

Plasma melatonin levels during the first hour after the seizure were significantly higher than those at 12 and 24 hours post-seizure in the patients ($P < 0.001$). The patient melatonin levels at 0 to 1 hour were not significantly different from those of the control group ($P = 0.97$); however, the 12- and 24-hours post-seizure melatonin concentrations were significantly lower than those of the controls ($P = 0.02$ for both; Table 2).

Plasma melatonin levels in patients with afebrile seizure according to antiepileptic drug use

The comparison of melatonin levels at 0 to 1 hour in patients with afebrile seizures revealed no significant difference between those who had and had not received antiepileptic medication ($P = 0.38$), suggesting that previous antiepileptic treatment had no effect on plasma melatonin levels.

Comparison of plasma melatonin levels during daytime and nighttime seizures

Comparing the melatonin levels at 0 to 1 hour in individuals with daytime (8 AM to 8 PM) and nighttime (8 PM to 8 AM) seizures, the time of day had no significant effect on melatonin levels in patients with afebrile ($P = 0.10$) or febrile seizures ($P = 0.27$). We also compared the plasma melatonin levels in the afebrile and febrile seizure groups at 0 to 1 hour and found no significant difference in melatonin levels between groups according to the time of seizure (daytime, $P = 0.98$; nighttime, $P = 0.83$). The comparison of control group melatonin levels with those of the daytime and nighttime seizure groups at 0 to 1 hour revealed no significant differences ($P = 0.41$ and 0.34, respectively; Table 3).

Discussion

Although the anticonvulsant effect of melatonin is not fully understood, the hormone has been shown to inhibit excitatory neurotransmission and to activate inhibitory neurotransmitters.[18,19] Antiepileptic drugs, such as valproic

TABLE 1.
Demographic Characteristics of the Study and Control Groups

	Patients ($n = 59$)	Controls ($n = 28$)	*P* Value
Age (years)	6.09 ± 4.46	7.27 ± 4.21	0.62
Weight (kg)	25.53 ± 14.20	28.78 ± 17.30	0.85
Sex (M/F)	31/28	16/12	0.22