

# Relationship between Juvenile Myoclonic Epilepsy and Melatonin

## *Juvenil Miyoklonik Epilepsi ve Melatonin İlişkisi*

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### Öz

**Amaç:** Melatoninun sirkadiyen ritmi düzenleyerek antikonvülsan ve nöroprotektif özelliklere sahip olduğu bulunmuştur. Bu etkisinden yola çıkarak Juvenil myoklonik epilepsili (JME) hastalar ve sağlıklı bireylerde melatonin serum düzeylerinin belirlenmesi amaçlanmıştır. JME'li hastalar ile sağlıklı bireylerdeki serum melatonin seviyelerini karşılaştırılan ilk çalışma olma özelliğini de taşımaktadır.

**Hastalar ve Yöntem:** Bu çapraz-kesitsel çalışmaya JME'li 30 hasta ve benzer cinsiyet ve yaş dağılımına sahip 30 sağlıklı kontrol dahil edildi. JME'li hastalar ve sağlıklı bireylerden, gece meydana gelen serum melatonin pik düzeyini ve sabahki en düşük serum melatonin düzeyini belirlemek üzere venöz kan örnekleri alınarak ELISA yöntemiyle çalışıldı.

**Bulgular:** Sağlıklı kontrollere kıyasla JME'li hastaların serum MELn ( $p = 0,002$ ) ve MELm ( $p = 0,001$ ) düzeyi daha düşük tespit edildi. Ayrıca JME'li hastalar ve kontrol grubu arasında MELn/MELm oranı ve MELn-MELm farkı açısından istatistiksel olarak anlamlı farklılıklar vardı (sırasıyla  $p = 0,005$  ve  $0,014$ ).

**Sonuç:** Elde edilen sonuçlar JME'li hastalar ve kontrol grubunda melatoninun sirkadien ritminin korunduğunu fakat hastalarda serum melatonin düzeylerinin kontrollere göre düşük seyrettiğini göstermektedir. Bundan dolayı JME'li hastalarda melatonin düzeyinin tespiti hem hastalık etyolojisinin belirlenmesine hem de gerektiğinde melatonin takviyesi yapılması ile gereksiz ve yüksek doz antiepileptik ilaç kullanımının engellenmesine katkı sağlayabilir.

**Anahtar Kelimeler:** Juvenil miyoklonik epilepsi, melatonin, sirkadiyen ritim

### Abstract

**Aim:** Melatonin has been found to have anticonvulsant and neuroprotective properties by regulating the circadian rhythm. Based on this effect, it was aimed to determine the serum levels of melatonin in patients with juvenile myoclonic epilepsy (JME) and healthy individuals. It is also the first study to compare serum melatonin levels in patients with JME and healthy individuals.

**Patients and Methods:** Thirty patients with JME and 30 healthy controls with similar gender and age distribution were included in this cross-sectional study. Venous blood samples were taken from patients with JME and healthy individuals to determine the peak serum melatonin level at night and the lowest serum melatonin level in the morning, and studied with the ELISA method.

**Results:** Compared to healthy controls, serum MELn ( $p = 0,002$ ) and MELm ( $p = 0,001$ ) levels of JME patients were determined to be lower than healthy controls. Moreover, there were statistically significant differences between MELn/MELm ratio and MELn-MELm difference between patients with JME and the control group ( $p = 0,005$  and  $0,014$ , respectively).

**Conclusion:** The results show that the circadian rhythm of melatonin is preserved in the patients with JME and the control group, but the serum melatonin levels in the patients are lower than in the controls. Therefore, the determination of melatonin level in patients with JME may contribute to both the determination of the etiology of the disease and the prevention of unnecessary and high-dose antiepileptic drug use by supplementing with melatonin when necessary.

**Key words:** Juvenile myoclonic epilepsy, melatonin, circadian rhythm

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## INTRODUCTION

Juvenile myoclonic epilepsy (JME) is an epileptic syndrome that occurs frequently during puberty and is classified separately within idiopathic generalized epilepsies by ILAE, which includes myoclonic jerks on awakening, generalized tonic-clonic seizures, and less frequently absence seizures (1,2). Although the pathophysiological mechanisms are unknown, there is some evidence of mild functional and structural disorders in the frontal lobes, and to a lesser extent extrafrontal (3). Lack of sleep increases the tendency to seizures in most patients (4). Other factors that cause seizures are alcohol intake, menstruation, fatigue, stress, tension, watching television, playing chess-like games, and irregular use of antiepileptic drugs (5). While clinical photosensitivity, that is, seizures triggered by flickering light, is seen approximately in 5%, photo-paroxysmal response is present at a rate of 30-40% in EEG (6).

The relationship between sleep and melatonin is well known. Melatonin, also known as the 'dark hormone', is a chronobiotic hormone synthesized in many organs such as the skin, lymphocytes and gastrointestinal tract, especially the pineal gland, and regulates major physiological processes such as sleep-wake cycle, pubertal development and seasonal adaptation in the body (7). Beyond being the major determinant of circadian rhythm, it is noteworthy that melatonin and analogous compounds using melatonin receptors are increasingly used in the management of depression, insomnia, Alzheimer's disease, diabetes, alopecia, obesity, migraine, cancer, immune and cardiac diseases (8,9). However, there are different data in the literature regarding the pathophysiology of epilepsy and the role of melatonin in its complementary treatment. In studies on epilepsy and melatonin, the relationship between different forms of epilepsy and circadian rhythm have been studied, and melatonin has generally been used as a determinant of the circadian rhythm (10,11).

Determining basal melatonin levels in JME patients can contribute to the understanding of JME pathophysiology and contribute to additional treatment modalities, however, no study has reported comparison of serum melatonin levels in patients with JME and healthy individuals in the literature. In this study, it was aimed to determine melatonin levels in JME.

## PATIENTS AND METHODS

The necessary ethics approval of the present study

was obtained from the "Institutional Ethics Committee of 'Institutional Ethics Committee of Meram Medical Faculty, Necmettin Erbakan University' enumerated as 2015/347 and dated as December 04th, 2015. A written consent form was then filled out by all participants, who were given in-depth information about the study that was to be conducted. The present study was conducted in accordance with Helsinki good clinical practice guidelines. (GCPG)

### Participants

Between January 2016 and December 2016, JME patients who were admitted for control purposes were considered for this prospective study. Out of this epilepsy patient population, 30 consecutive JME patients were selected in accordance with the inclusion criteria. Healthy controls consisted of healthy individuals, mostly university hospital employees, without a history of epilepsy matching positively with JME patients age and sex criteria, and meeting all inclusion criteria. Neurological and physical examinations of patients diagnosed with JME were performed by the same neurologist in order to avoid evaluation bias. Demographic and clinical characteristics of the patients were recorded.

All patients in the JME group were receiving anti-epileptic drugs (AEDs) on daily basis administered orally. Out of these were valproic acid (VPA) (18 patients); levetiracetam (LEV) (7 patients); lamotrigine (LTG) (4 patients), and zonisamide (ZNS) intake (1 patient). The distribution of AED use of JME patients is presented in Table 1.

The inclusion criteria for the JME patient group were as follows; voluntary enrolment; age between 18 and 45 years; JME diagnosis as described in the 1989 revision to the ILAE criteria for clinical information and in EEG tests, lack of any chronic (mental retardation, insomnia, ie) or acute medical condition (status epilepticus, head injury, ie) other than JME as confirmed through previous medical reports and clinic examinations; no use of medications including antiaggregants, anticoagulants, beta blockers, non-steroidal anti-inflammatory drugs, products containing melatonin, corticosteroids, selective serotonin re-uptake inhibitors and antipsychotics; and no previous report of illicit drug or substance abuse or addiction. In addition, the participants were warned that sleep deprivation, excessive exercise, caffeine and alcohol use should be avoided for 72 hours before sampling, as it may affect melatonin levels and cause deviations from the basal value.

**Table 1.** The demographic, clinical and laboratory characteristics of patients and controls

	JME Patients (n=30)	Controls (n=30)	p value
Age, years, median [25th, 75th]	24.0 [20.0, 28.7]	24.0 [21.5, 29.0]	0.672*
Age of onset, years, median [25th, 75th]	16.5 [13.0, 20.2]		
Disease duration, years, median [25th, 75th]	7.0 [2.7, 10.2]		
Gender			
Male, n, %	16, 53.3%		
Female, n, %	14, 46.7%	14, 46.7%	1.000**
MELn (pg/mL), median [25th, 75th]	74.5 [53.7, 441.2]	590.0 [107.2, 760.5]	0.002*
MELm (pg/mL), median [25th, 75th]	35.5 [25.7, 226.2]	324.5 [78.2, 324.5]	0.001*
MELn / MELm, median [25th, 75th]	2.0 [1.8, 2.1]	1.7 [1.6, 1.9]	0.005*
MELn – MELm, median [25th, 75th]	39.5 [28.0, 205.7]	267.0 [38.5, 406.0]	0.014*
AED use			
VPA, n, %	18, 60.0%		
LEV, n, %	7, 23.3%		
LTG, n, %	4, 13.3%		
ZNS, n, %	1, 3.3%		

\* Tested using Mann-Whitney Test

\*\* Tested using Pearson's Chi – squared test

Bold: statistically significant results

### Measurement of melatonin

Venous blood samples were taken from JME patients and healthy individuals at 03:00 under dim light to determine the peak serum melatonin level at night, and at 10:00 to determine the lowest serum melatonin level in the morning. The blood samples were centrifuged at 4°C and 1000 g speed for 10 minutes in a Hettich Rotina 46R (Hettich Zentrifugen, Tuttlingen, Germany) brand refrigerated centrifuge device, and the serums were separated. Serum samples were stored in New Brunswick U570 (New Brunswick Scientific, New Jersey, USA) refrigerator at -80°C until the parameters were studied. Melatonin (YH Biological Technology Company, Shanghai,

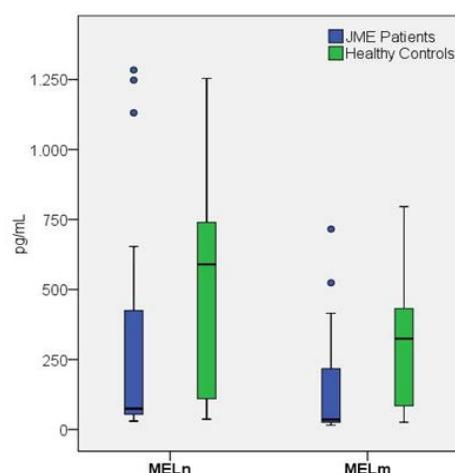
China) levels in serum samples were studied by ELISA (Enzyme-linked immunosorbent assay) method. Serum melatonin levels were calculated according to the absorbance concentration calibration charts using the Biotek ELX 50 microplate washer (BioTek Instruments, Vermont, USA) and the Biorad Microplate absorbance reader xMark (Bio-Rad Laboratories, California, USA) system.

### Statistical analysis

The data obtained in the present study were analyzed using IBM SPSS statistics software version 20.0 (IBM Corp., Armonk, NY, USA). Using the Kolmogorov-Smirnov Test, normality was checked for each continuous variable. Non-normally distributed continuous variables were expressed as median [25th, 75th percentiles]. Categorical variables were expressed as numbers and percentages. The Mann-Whitney Test was used to compare non-normally distributed continuous variables between two independent groups. Categorical data between two groups were compared using Pearson's Chi-Square Test. A 2-tailed p<0.05 threshold value was considered for statistical significance.

### RESULTS

The median [25th, 75th percentile] age of the 30 JME patients was 24.0 [20.0, 28.7] years; 14 (46.7%) of them were female and 16 (53.3%) were male. The median [25th, 75th percentile] age of the 30 healthy controls was 24.0 [21.5, 29.0] years; 14 (46.7%) were female and 16 (53.3%) were male. There were no statistically significant differences between the JME patients and those in the control group in terms of age and gender (p = 0.672 and 1.000, respectively).

**Figure 1.** Median levels of MELn and MELm in patient and control groups.

Demographic and clinical characteristics of the participants are presented in Table 1.

The median [25th, 75th percentile] MELn level was 74.5 [53.7, 441.2] (pg/mL) in the JME patients, and 590.0 [107.2, 760.5] (pg/mL) in the control group. The median [25th, 75th percentile] MELm level was 35.5 [25.7, 226.2] (pg/mL) in JME patients and 324.5 [78.2, 324.5] (pg/mL) in the control group. There were statistically significant differences in MELn and MELm levels between the JME patients and control group ( $p = 0.002$  and  $0.001$ , respectively) (Figure 1). MELn and MELm levels for JME patients and control participants are presented in Table 1.

The median [25th, 75th percentile] MELn/MELm ratio was 2.0 [1.8, 2.1] in JME patients, and 1.7 [1.6, 1.9] in the control group. The median [25th, 75th percentile] MELn-MELm difference was 39.5 [28.0, 205.7] in JME patients and 267.0 [38.5, 406.0] in the control group. There were statistically significant differences in terms of MELn/MELm ratio and MELn-MELm difference between JME patients and those in the controls ( $p = 0.005$  and  $0.014$ , respectively) (Table 1).

## DISCUSSION

We found statistically significant lower serum melatonin levels measured at night and in the morning in JME patients compared to healthy controls. The data obtained shows that the circadian rhythm of melatonin is preserved in the patient and control groups, but melatonin levels are lower in the patient group. Low melatonin levels in JME patients may play a triggering role by impairing sleep quality, or it may be a result of the existing disease. This is the first study to compare serum melatonin levels in patients with JME and healthy individuals. It is thought that the results of the study may reveal new information about the pathophysiology of JME and the role of melatonin in complementary therapy.

It is clearly known that the hormone melatonin, whose serum levels start to rise with the onset of darkness in mammals and rapidly decrease with the dawn, is closely related to the onset, maintenance, quality of sleep and the determination of the circadian rhythm (12). Decreased melatonin production and disruption of nocturnal melatonin secretion have been associated with various central nervous system diseases such as stroke, obsessive-compulsive disorder, and mood disorders (13). Due to its antioxidant effects, melatonin is used in the treatment of many neurological diseases such as epilepsy, amyotrophic

lateral sclerosis, Alzheimer's disease, ischemic injury and head trauma due to its neuroprotective effects (14). Mitochondrial dysfunction and glutamate overactivity, in which free radicals are involved in neuronal loss, are associated with disease progression in most of these diseases (8).

Studies of melatonin levels in humans are generally concerned with melatonin hormone physiology, metabolism and its role in the circadian rhythm. In studies related to melatonin epilepsy, the anticonvulsant and/or pro-convulsant role of melatonin and the effects of exogenous melatonin supplementation on the frequency and severity of seizures have been researched (15-18). Only very few studies have compared baseline melatonin levels between epilepsy patients and healthy individuals. In addition, there are great methodological differences between studies. Whereas some of these studies have investigated plasma or serum melatonin levels, others have investigated salivary melatonin levels. In some, the melatonin metabolite excreted in the urine was additionally measured. The biochemical methods used in the measurements of melatonin in the studies also do show a wide variety (such as RIA, ELISA, Atomic absorption, HPLC), and the commercial kits for each different method used also show differences among themselves. For this reason, the information related to basal melatonin levels, which are currently very few in the literature, show great differences among each other.

Low levels of melatonin have been reported in some types of epilepsy, and data obtained from human support that melatonin exerts an anticonvulsant effect by both reducing seizure frequency and improving EEG abnormality. Hence, its combination with other antiepileptic drugs may be beneficial (19). In a case report of a severe myoclonic epilepsy case; it has been reported that seizures that cannot be controlled with combined antiepileptic therapy could be controlled after melatonin is administered combined with phenobarbital (20). Similarly, Fauteck et al. (17) claimed that a single dose of 5-10 mg melatonin given in the evening can reduce the incidence of epileptic attacks in children and that melatonin can be used as an antiepileptic drug. There are also different data on the pathophysiology of epilepsy and the place of melatonin in its complementary treatment. Mahyar A. et al. (15) performed serum melatonin measurements in 37 children with simple febrile seizures, 37 children with complex febrile seizures, 37 children with epilepsy, and 37 children with fever only as controls,

they determined that there was no difference between the children with seizures and those in the control group in terms of serum melatonin levels. In addition, no significant difference was found between the groups in the seizure population (15). On the other hand, Guo et al., (21) reported that serum melatonin levels were low in children with epilepsy or complex febrile seizures, and they suggested that external melatonin supplementation may be beneficial in the treatment of epilepsy and febrile seizures in these children. In the study conducted by Yalin et al., (16) plasma melatonin levels at four different times of the day were compared in 10 participants with diurnal complex partial epilepsy, 10 with nocturnal complex partial epilepsy, and 10 healthy participants, and it was determined that melatonin levels in patients with both nocturnal complex partial epilepsy and diurnal complex partial epilepsy were found to be between 10:00 a.m. and 10:00 p.m. and between 01:00-05:00 a.m. always lower than those in the control groups, and the lowness at 10:00 a.m. was found to be statistically significant (16). In the present study, statistically significant lower serum melatonin levels were measured both at night and in the morning in the JME patients compared to those in the control group. Although melatonin levels were lower in the patient group, it was observed that the circadian rhythm of melatonin was preserved in both our patients and the control groups.

Bazil et al. (22) reported that basal melatonin levels in the saliva of patients with refractory temporal lobe epilepsy were lower than that of the controls' and increased threefold after seizure. They interpreted this finding as the anticonvulsant effects of melatonin (22). In another study in 54 children with convulsive seizures (febrile and epileptic), it was found that serum melatonin levels increased during seizure attacks and returned to normal level after 1 hour (23). Researchers have commented that the increase in melatonin produced by a convulsive seizure may express the response to the seizure in the body and aim to maintain homeostasis (23). However, Schapel et al. (24) reported that urinary 6-sulphatoxymelatonin excretion was increased in 30 untreated epilepsy patients with active epilepsy compared to healthy controls (24). They interpreted this situation as an increase in melatonin production in patients with untreated active epilepsy and phase differences compared to controls (24). On the contrary, Rao et al. (25) determined that serum melatonin levels did not change during and 2 hours after seizures and

remained within normal limits as in healthy individuals. The fact that seizures are under control in almost all of our patients with JME and the lack of sleep deprivation in all of them within the last 72 hours eliminates the possibility of postictal melatonin elevation.

The studies mentioned above clarify that the melatonin levels may differ according to the type of epilepsy and it is still not clear whether there is a relationship between these differences in melatonin levels and antiepileptic treatment. Among all epilepsy syndromes, photosensitivity and sensitivity to sleep deprivation are well known in JME patients. Melatonin measurements in JME patients have been mostly conducted within the context of seizure and circadian rhythm relationship and as a determinant of the circadian rhythm (26). In this regard, the present study is the first to directly compare serum melatonin levels in patients with JME and healthy individuals.

The cross-sectional nature of the study and the small patient cohort are an important limitation and may affect the reliability of the present study's findings. There are also some inherent limitations in the present study, such as the fact that the contribution of additional melatonin to reduce the dose of antiepileptic therapy was not evaluated. Melatonin replacement in JME patients, reduction in seizure frequency and the effect of using lower doses in the use of AEDs and its contribution to the transition from combined therapy to mono-therapy may be the subject of further research. The present study excluded the evaluation of melatonin metabolites excreted in the urine. Despite all limitations of the present study, determination of statistically significant lower serum melatonin levels measured at night and in the morning in patients with JME will contribute to the literature both in illuminating the pathophysiology of the disease and in planning treatment management.

## CONCLUSION

In this prospective study, it was determined that the melatonin levels of JME patients were lower compared to healthy controls. We suggest that melatonin levels should be studied in patients presenting JME for both determining disease etiology and preventing unnecessary use of high-dose antiepileptic drugs via melatonin supplementation.

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