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Research Article

Assessment of Melatonin Circadian Rhythm in Epileptic Children -

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ABSTRACT

Melatonin suppresses neuronal excitation by inhibiting glutamate and neuronal Nitric Oxide (NO) synthase activity and decreasing NO production via increased cell membrane permeability of chlorine through Gamma-Aminobutyric Acid (GABA) chloride channels. The relationship between sleep and epilepsy is complicated and reciprocal, Sleep affects epilepsy, and epilepsy, in turn, affects sleep. Seizure disorders exhibit a marked responsiveness to the circadian rhythm, and human as well as experimental models reveal similar properties with respect to periodicity.

Method: This case control study was done in Pediatrics Neurology outpatient clinic, Children's Hospital, Ain Shams University. It included 47 patients and 47 age and sex matched healthy children. All cases were subjected to complete history taking, physical examination, neurological examination, laboratory investigations (diurnal and nocturnal serum melatonin levels), and EEG.

Results: The melatonin circadian rhythm was not grossly disturbed in studied children with epilepsy as compared to controls. Our data revealed that children with epilepsy had significantly higher serum melatonin (diurnal-nocturnal) levels compared to control group. The percentages of generalized seizures were higher than focal seizures. Melatonin levels were significantly higher in epileptic children compared to control group. Melatonin levels were significantly higher in epileptic children with refractory seizures than in epileptic children with controlled seizures.

Conclusion: The circadian rhythm of melatonin was not grossly disturbed in epileptic children as compared to healthy controls. The significantly higher serum melatonin concentrations in epileptic children as compared to healthy individuals brought an observation that melatonin may serve as a natural downregulator of cerebral epileptogenic activity. In the most typical cases of epilepsy in childhood, the Melatonin system responds to the light/dark cycle.

INTRODUCTION

Epilepsy is a condition characterized by recurrent (two or more) seizures unprovoked by an immediate identifiable cause. An epileptic seizure is a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain [1]. Epilepsy starts in childhood in 60% of cases and most of the clinically significant aspects, serial seizures and Status Epilepticus (SE) are common in childhood; 40% of Status Epilepticus occurs in children under two years of age and 75% of status epilepticus is the first seizure presentation in a child [2]. The relationship between sleep and epilepsy is complicated and reciprocal, Sleep affects epilepsy, and epilepsy, in turn, affects sleep. Seizure disorders exhibit a marked responsiveness to the circadian rhythm, and human as well as experimental models reveal similar properties with respect to periodicity. Experimental evidence indicates that the pineal gland and melatonin have a major influence on the control of brain electrical activity and have been shown to be involved in seizure and sleep mechanisms [3].

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine produced primarily by the pineal gland. Its production is regulated by light and the retinohypothalamic tract. It is released in circadian rhythm with peak concentration at night [4]. Melatonin has been associated with many different functions such as sleep promotion, control of biological rhythms, hormonal inhibition and inhibitions of central nervous system regulatory mechanisms. Furthermore, an anticonvulsant effect of melatonin has been reported [5].

Melatonin suppresses neuronal excitation by inhibiting glutamate and neuronal Nitric Oxide (NO) synthase activity and decreasing NO production via increased cell membrane permeability of chlorine through Gamma-Aminobutyric Acid (GABA) chloride channels. Melatonin secretion depends on age, as the highest values reported of its concentration are detected between 1 and 7 years of age, Melatonin secretion in epilepsy shows diverse results: higher nocturnal melatonin concentrations, higher melatonin concentration after seizures, or loss of the characteristic diurnal rhythm of secretion [6].

AIM OF THE WORK

The aim of this study is to assess serum melatonin levels and melatonin circadian rhythm in epileptic children.

PATIENTS AND METHODS

A case control study was carried out in Pediatrics Neurology outpatient clinic, Children's Hospital, Ain Shams University, in the period from january 2018 till january 2020. It included 94 volunteers (47 epileptic children, 47 healthy children). after obtaining Institutional Review Board approval (IRB) from our hospital and informed consent from parents before the study. The study included 47 patients (23 males and 24 females) their age ranged from 1.5 to 11 years old with (mean ± SD of 5.81 ± 2.6) and 47 controls age- and sex-matched to the study patients.

Patients

Forty seven patients with epilepsy admitted in the neurology unit of pediatric university hospital were enrolled in the study.

Inclusion criteria - Cases: Children diagnosed with epilepsy between the age of 1 year and 12 years.

Exclusion criteria

-Patients with morphological brain abnormalities

-patients with progressive brain disorders

-Patients with severe comorbidities such as organ failure, cancer, inborn errors of metabolism and autoimmune diseases.

A written consent was taken from the parents of each case. The study was approved by our ethical committee.

Controls: 47 children who were admitted to our Children's hospital for other indications rather than epilepsy or seizures Age, gender and weight matched to the studied patients.

Methods

All patients were subjected to the following

1. Full history taking
2. Full general examination.
3. Full neurological examination.
4. Investigations:

a. Routine laboratory tests: CBC, serum electrolytes, liver and kidney function testes

b. Serum diurnal and nocturnal melatonin levels.

c. Brain imaging (CT or MRI)

d. Electroencephalography (EEG)

Sample collection: Nocturnal and diurnal samples of 3 ml venous blood were taken from all patients and controls then centrifuged. The serum was then poured into an acid-washed tube and kept in the refrigerator at a controlled temperature (-20˚C). All conditions such as postural conditions and environmental lighting were the same for all groups during blood sampling. Measurement of serum melatonin was performed by Enzyme Linked Immunosorbent Assay (ELISA) with a kit (human melatonin ELISA kit).

Reagent preparation: Incubation was done then Melatonin (MT) antibodies labeled with biotin and combined with streptavidin-HRP was added to form immune complex, then re-incubation and washing was done to remove the uncombined enzyme. Chromogen solution A & B were added to change color of liquid into blue then into yellow. Finally, the chroma of color and concentration of Human Substance Melatonin (MT) of sample were positively correlated.

Assay Procedure

Add sample 40 µl, and then add both MT–antibody 10 µl and Streptavidin-HRP 50 µl. Then seal the sealing membrane, and gently shaking, incubated 60 minutes at 37.

The washing concentrate was diluted 30 times with distilled water then sealing membrane was removed and liquid was drained.

Chromogen solution A 50 µl was added and mixed to chromogen solution B 50 µl then incubated for 10 minutes at 37˚C away from light. Stop solution 50 µl was added into each well to stop the reaction.

Blank well was taken as zero, optical density under 450 nm wave length was measured within 15 minutes after the stop solution was added.

CALCULATION OF RESULTS

Take the standard density as the horizontal the OD value for the Vertical draw the standard curve on graph paper, Find out the corresponding density according to the sample OD value by the Sample curve (the result is the sample density) or calculate the straight line regression equation of the standard curve with the standard density and the OD value, with the sample OD value in the equation, calculate the sample density

Sensitivity and assay range

Sensitivity: 0.453 ng/L: The sensitivity of this assay was defined as the lowest protein concentration that could be differentiated from zero. It was determined by subtracting two standard deviations to the mean optical density value of twenty zero standard replicates and calculating the corresponding concentration.

Assay range: 0.5 ng/L to 120 ng/L.

Statistical analysis

All data were analyzed SPSS 18.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium) Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage).

RESULTS

There is statistically higher significant serum diurnal and nocturnal melatonin levels in the studied cases versus the controls ($p < 0.001$) . No significant statistical among the studied groups as regards age, gender and family history. The cases and control groups are matched as regards age, sex and family history of epilepsy . Idiopathic epilepsy as the most predominant etiology of seizures, GTCC as the most common seizure type account for 53.2% of cases followed by complex partial seizures, mean age of onset of seizures 3.43 ± 2.38 years, generalized epileptogenic activity was the most common EEG finding account for 44.7% of the studied cases no significant statistical difference of serum (diurnal & nocturnal) melatonin levels concerning gender of studied cases. This table shows no significant statistical difference of serum diurnal & nocturnal melatonin levels among different age group of the studied cases.

No significant statistical difference of serum diurnal and nocturnal melatonin levels as regards family history of the studied cases. No significant statistical difference between different seizure types except for GTCs where nocturnal serum melatonin levels were significantly lower in comparison to other seizure types. No statistical significant difference of serum melatonin levels as regards age of onset of epilepsy. No significant statistical difference of serum diurnal and nocturnal melatonin levels as regards duration of the disease. Controlled seizures were more common than refractory seizures in the studied cases.

Sodium valproate was the most common Antiepileptic Drug (AED) used in treatment of the studied cases accounting for 70.2% of total cases followed by Levetiracetam accounting for 59.6% of cases. There was statistically significant higher serum melatonin levels (diurnal-nocturnal) in cases with refractory epilepsy than cases with controlled epilepsy ($p < 0.001$). No significant statistical difference of serum diurnal and nocturnal melatonin levels among cases with diurnal seizures and those free of diurnal seizures. Cases with nocturnal seizures have statistically significant high diurnal melatonin levels and significantly higher serum nocturnal melatonin level as compared to cases free of nocturnal seizures (Tables 1-8).

DISCUSSION

Epilepsy is the most common childhood chronic neurological disease characterized by an enduring predisposition to generate epileptic seizures that disrupt the nervous system and can cause mental and physical dysfunction**.** The importance of both recognizing desynchronized daily rhythms during illness and the role of circadian rhythm in general pediatric care has been described in the literature [7]**.** Melatonin plays a key role in regulating the circadian rhythm nd is implicated in the regulation of multiple other physiologic functions, e.g., sleep promotion, mood swings, the modulation of both cellular and humoral immunity, anti-inflammatory actions and antioxidative processes [8]**.** The aim of this study was to assess serum melatonin levels and melatonin circadian rhythm in epileptic children. In our

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study there was no statistically significant difference between cases and controls as regard age, sex and family history.

In our study we found that idiopathic seizures were the most common cause of epilepsy in the studied cases accounting for 78.7%

Table 1: Comparison between cases and control as regards demographic data.

Demographic data	Cases (*N* = 47)		Control (*N* = 47)		Test	p-value (Sig.)
	No.	%	No.	%		
Sex						
Male	23	48.90%	24	51.10%	0.043 ‡	0.837
Female	24	51.10%	23	48.90%		(NS)
Age (years)						
Mean ± SD	5.81 ± 2.60		5.81 ± 2.63		-0.030	0.976
Median (Range)	6 (1.50–11)		6 (1.50–11)			(NS)
< 3 years	5	10.60%	7	14.90%	0.382 ‡	0.826
3-6 years	22	46.80%	21	44.70%		(NS)
> 6 years	20	42.60%	19	40.40%		
Family History						
Negative	41	87.20%	46	97.90%	3.859 ‡	0.111
Positive	6	12.80%	1	2.10%		(NS)

• Mann Whitney U test
‡ Chi-square test
$p < 0.05$ is significant
Sig.: significance

Table 2: Clinical characters of cases (*N* = 47).

Clinical data	Cases (*N* = 47)	
	No.	%
Etiology		
Idiopathic	37	78.70%
Symptomatic	10	21.30%
Type of seizures		
Absence	1	2.10%
Complex partial	14	29.80%
Focal epilepsy with 2ry generalization	7	14.90%
GTCC	25	53.20%
Age at onset (years)		
Mean ± SD	3.43 ± 2.38	
Median (Range)	3 (0.50–10.50)	
< 3 years	20	42.60%
3-6 years	23	48.90%
> 6 years	4	8.50%
Duration of the disease (years)		
Mean ± SD	2.37 ± 1.88	
Median (Range)	2 (0.50–9)	
< 1 year	6	12.80%
1-6 years	28	59.60%
3-6 years	10	21.30%
> 6 years	3	6.40%
EEG		
Normal	6	12.80%
Focal	20	42.60%
Generalized	21	44.70%
Diurnal seizure		
No	2	4.30%
Yes	45	95.70%
Nocturnal seizure		
No	25	53.20%
Yes	22	46.80%

Table 3: Comparison between cases and control as regard serum melatonin (ng/L).

Serum melatonin (ng/L)	Cases (N = 47)	Control (N = 47)	Test	p-value (Sig.)
Diurnal				
Mean ± SD	27.07 ± 27.23	10.42 ± 3.76	-5.056	< 0.001
Median (Range)	15 (6.60 – 124)	9.30 (4.60 – 24)		(HS)
Nocturnal				
Mean ± SD	78.84 ± 42.45	37.14 ± 10.10	-5.052	< 0.001
Median (Range)	72 (15.90 – 154)	37.80 (20.70 – 62)		(HS)
Difference				
Mean ± SD	51.77 ± 33.73	26.71 ± 9.42	-4.144	< 0.001
Median (Range)	46.50 (4.40 – 146.40)	25.70 (8.30 – 52.70)		(HS)

• Mann Whitney U test
$p < 0.05$ is significant
Sig.: significance

Table 4: Relation between sex , age ,family history, aetiology and serum melatonin (ng/L).

Sex	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Male	23	22.01 ± 18.02	70.46 ± 45.65	48.45 ± 33.50
Female	24	31.92 ± 33.50	86.87 ± 38.39	54.95 ± 34.36
Test		-1.362	-1.618	-0.649
p-value (Sig.)		0.173 (NS)	0.106 (NS)	0.516 (NS)
Age group	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
<3 years	5	33.04 ± 50.90	60.94 ± 45.47	27.90 ± 22.69
3-6 years	22	24.17 ± 21.24	81.13 ± 46.65	56.95 ± 35.97
>6 years	20	28.76 ± 27.00	80.80 ± 37.80	52.03 ± 32.17
Test		1.998	1.183	3.46
p-value (Sig.)		0.368 (NS)	0.554 (NS)	0.177 (NS)
Family history	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Negative	41	28.09 ± 28.71	78.00 ± 41.25	49.90 ± 32.07
Positive	6	20.10 ± 12.70	84.60 ± 54.09	64.50 ± 44.90
Test		-0.383	-0.191	-0.797
p-value (Sig.)		0.702 (NS)	0.848 (NS)	0.425 (NS)
Etiology	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Idiopathic	37	25.29 ± 27.34	74.07 ± 42.34	48.77 ± 32.93
Symptomatic	10	33.63 ± 27.17	96.49 ± 40.00	62.86 ± 36.12
Test		-1.053	-1.469	-1.092
p-value (Sig.)		0.292 (NS)	0.142 (NS)	0.275 (NS)

• Mann Whitney U test
$p < 0.05$ is significant
Sig.: significance©

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of total cases. This disagreed with Paprocka, et al. [6] who investigated melatonin levels in childhood refractory epilepsy, symptomatic epilepsy account for 51.4% of the studied cases.

In our study the most common type of seizures was generalized tonic colonic convulsions accounting for 53.2% of the studied cases followed by complex partial seizures accounting for 29.8% of cases. We found that melatonin circadian rhythm was not grossly disturbed in all the studied patients and controls.

In concordance to our finding Yalyn, et al. [9] observed that epileptic children and controls did not differ with respect to circadian rhythm. Yalyn, et al. [9] Compared circadian profiles of melatonin serum secretion in patients with nocturnal and diurnal complex partial seizures with those in control group. Each group included 10

Table 5: Relation between type of seizures , age of onset , duration of the disease and serum melatonin (ng/L).

Type of seizures	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Absence	1	55.9	106.3	50.4
Complex partial	14	34.56 ± 32.38	95.16 ± 46.90	60.60 ± 38.77
Focal epilepsy with 2ry generalization	7	45.58 ± 43.78	113.37 ± 39.37	67.78 ± 48.07
GTCC	25	16.53 ± 9.53	58.93 ± 30.46	42.40 ± 24.03
Test‡		4.346	11.227	2.683
p-value (Sig.)		0.226 (NS)	0.011 (S)	0.443 (NS)
Age at onset	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
< 3 years	20	30.29 ± 34.03	89.92 ± 49.20	59.62 ± 44.86
3-6 years	23	26.70 ± 22.46	73.53 ± 37.40	46.83 ± 22.68
> 6 years	4	13.05 ± 0.78	53.95 ± 13.69	40.90 ± 13.37
Test‡		1.268	2.513	0.493
p-value (Sig.)		0.531 (NS)	0.285 (NS)	0.624 (NS)
Duration of the disease	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
< 1 years	6	12.86 ± 3.41	51.83 ± 22.32	38.96 ± 21.15
1-3 years	28	28.56 ± 27.52	83.71 ± 43.66	55.14 ± 33.21
3-6 years	10	25.74 ± 25.25	67.85 ± 41.08	42.11 ± 26.68
< 6 years	3	45.96 ± 52.42	124.06 ± 26.29	78.10 ± 69.32
Test‡		2.85	6.298	2.1
p-value (Sig.)		0.415 (NS)	0.098 (NS)	0.552 (NS)

‡ Kraskall Wallis H test
$p < 0.05$ is significant
Sig.: significance

Table 6: Relation between EEG findings and serum melatonin (ng/L).

EEG findings	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Normal	6	14.88 ± 5.79	52.96 ± 34.72	38.08 ± 29.79
Focal	20	39.75 ± 36.09	105.90 ± 40.86	66.16 ± 40.19
Generalized	21	18.47 ± 13.29	60.45 ± 31.13	41.98 ± 22.30
Test‡		4.026	12.884	4.567
p-value (Sig.)		0.134 (NS)	0.002 (S)	0.102 (NS)

‡ Kraskall Wallis H test
$p < 0.05$ is significant
Sig.: significance

Table 7: Distribution antiepileptic drugs, Distribution of response to AEDs among the studied cases ($N = 47$).

Antiepileptic drugs	Cases ($N = 47$)	
	No.	%
Sodium Valproate	33	70.20%
Levetiracetam	28	59.60%
Phenytoin	10	21.30%
Topiramate	1	2.20%
Clonazepam	9	19.10%
Carbamazepine	16	34%
Response to AEDs	**Cases ($N = 47$)**	
	No.	**%**
Controlled	31	66%
Refractory	16	34%

Table 8: Relation between response to AEDs , Relation between diurnal seizure , nocturnal_seizure and serum melatonin (ng/L) and serum melatonin (ng/L).

Response to AEDs	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
Controlled	31	14.07 ± 4.89	53.65 ± 25.67	39.58 ± 22.09
Refractory	16	52.25 ± 34.65	127.64 ± 18.93	75.39 ± 40.14
Test		- 4.177	- 5.423	- 3.11
p-value (Sig.)		< 0.001 (HS)	< 0.001 (HS)	0.002 (S)
Diurnal seizure	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
No	2	16.70 ± 2.40	73.35 ± 25.95	56.65 ± 28.35
Yes	45	27.53 ± 27.75	79.08 ± 43.21	51.55 ± 34.21
Test		- 0.395	- 0.026	- 0.527
p-value (Sig.)		0.693 (NS)	0.979 (NS)	0.598 (NS)
Nocturnal seizure	N	Serum melatonin (ng/L)		
		Diurnal	Nocturnal	Difference
		Mean ± SD	Mean ± SD	Mean ± SD
No	25	15.43 ± 9.47	52.55 ± 28.60	37.11 ± 23.03
Yes	22	40.29 ± 34.31	108.71 ± 35.43	68.42 ± 36.61
Test		- 2.986	- 4.457	- 3.102
p-value (Sig.)		0.003 (S)	< 0.001 (HS)	0.002 (S)

• Mann Whitney U test
$p < 0.05$ is significant
Sig.: significance

subjects and serum samples for melatonin determination were taken four times during a 24-h period: at 10 a.m., 10 p.m., 1 a.m. and 5 a.m. The authors concluded that the circadian profile of melatonin secretion was identical in all studied groups. Average circadian melatonin concentration in serum from patients suffering from either diurnal or nocturnal complex partial seizures was significantly lower (as compared to control) only at 10 a.m [9].

In accordance to our findings Praninskiene, et al. [10] studied Melatonin (MLT) system in children with epilepsy. Diurnal patterns of salivary MLT, urinary metabolite 6-sulphatoxymelatonin, core body temperature, pulse and blood pressure were measured in 51 children with epilepsy (6.6-17.9 years) and 29 comparison children (5.5-17.3 years) [10].

In our study, we observed that serum diurnal and nocturnal melatonin levels were significantly higher in epileptic children compared to the healthy controls ($p < 0.001$). Our findings agreed with Eid, et al. [11] found that the mean serum levels of melatonin were significantly higher in both untreated and treated epileptic children compared to controls. However its levels in treated children were significantly lower compared to untreated children. The authors concluded that overproduction of melatonin may possibly be an attempt by the brain cells to produce a natural down regulator of cerebral epileptiform activity [11].

Melatonin appears to enhance the major neurochemical GABA, whose function is to stop or inhibit seizures. In addition, melatonin blocks the excitatory neurotransmitter glutamate which promotes seizures [9].

Melatonin is an anti-oxidant, with potent free radical scavenging properties, it scavenges oxygen free radicals like superoxide radical, hydroxyl radical, peroxyl radical and peroxynitrite anion. Melatonin can also enhance the antioxidative potential of the cell by stimulating the synthesis of antioxidative enzymes like Superoxide Dismutase (SOD) and glutathione peroxidase [12]**.** The antiepileptic effect of melatonin was confirmed by Peled, et al. [13] who indicated that the anticonvulsant proprieties of melatonin are due to antioxidant activity, increase of brain Gamma-Aminobutyric Acid (GABA) concentration, inhibition of calcium influx into neurons, and decreased neuronal nitric oxide generation [13]**.**

Our findings disagreed with Orcun, et al. [14] who found that basal melatonin levels were decreased in patients with afebrile and febrile seizures compared to healthy children and that melatonin values increased during and immediately following seizure and then decreased to a lower level than that of healthy children by 24 hours after a seizure. They further added that melatonin may act as an endogenous anticonvulsant [14].

In contrast to our findings Mahyar, et al. [15] investigated serum melatonin levels in 111 children with simple Fs**,** complex FS and epilepsy showed that there are no associations between serum melatonin levels and simple or complex FS and epilepsy. They concluded that melatonin plays no role in these convulsive disorders [15].

In our study there was no statistically significant difference between male and female cases as regards serum diurnal and nocturnal melatonin levels. In our study there was no statistical significant difference between cases with positive family history and those with negative family history of epilepsy as regards serum diurnal and nocturnal melatonin levels. In our study there was no statistical significant difference between cases with idiopathic epilepsy and those with symptomatic epilepsy as regards serum diurnal and nocturnal melatonin levels. In our study there was no statistical significant difference of serum diurnal and nocturnal melatonin levels in different type of seizures except for nocturnal serum melatonin levels were significantly lower in cases with generalized tonic colonic convulsions ($p < 0.05$). This can be attributed to the effect of sodium valproate used in treatment of cases of GTCs on melatonin secretion and this agreed with Monteleone, et al. [16] who found that nocturnal melatonin levels were suppressed by evening administration of sodium valproate to healthy subjects [16].

In our study we found that plasma melatonin concentrations (diurnal and nocturnal) were not significantly different between different age groups. As well as with duration of the disease. We found that serum nocturnal melatonin levels were significantly higher in cases with focal epileptogenic activity on EEG.

In our study significant higher diurnal and nocturnal melatonin levels were detected in cases with nocturnal seizures while in cases with diurnal seizures no significant difference of melatonin levels in comparison to cases free of diurnal seizures. By contrast to our findings Yalyn, et al. demonstrated that there are no differences in melatonin levels between patients with diurnal and those with nocturnal complex partial epilepsy [9].

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