

Serum Levels of Melatonin and Sleep Evaluation Scales in the Diagnosis of Sleep Disorders in Patients with Idiopathic Parkinson's Disease

İdiyopatik Parkinson Hastalığında Görülen Uyku Bozukluklarının Tanısında Uyku Testleri ve Serum Melatonin Düzeyleri

Hasan Armağan UYSAL, Bedile İrem TİFTİKÇİOĞLU, Levent ÖCEK, Yaşar ZORLU

İzmir Tepecik Research and Training Hospital, Neurology Clinic, İzmir, Turkey

ABSTRACT

Introduction: Sleep disturbances, such as difficulty in initiation of sleep, decrease in total sleep duration and efficacy, frequent awakenings, and increased daytime sleepiness are among the most common non-motor symptoms in patients with idiopathic Parkinson's disease (PD). However, patients usually do not consider these symptoms as important as their motor symptoms, and do not complain. We aimed to investigate PD patients for subtle sleep disturbances using sleep evaluation scales, and to evaluate the relationship between these tests and the serum levels of melatonin during night-sleep.

Methods: A total of 40 PD patients (19, female), older than 50 years, registered in our "Movement Disorders Out-patient Clinic", and 40 healthy, age and sex-matched control subjects (20, female) were included in the study. All subjects were assessed using Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Serum melatonin levels during night-sleep were measured in blood samples taken at 00:00 and 05:00 hours in every subject. Both groups were compared for demographical data, sleep evaluation scales and serum levels of melatonin.

Results: Patients with PD had significantly higher scores in PSQI and ESS than the healthy controls ($p < 0.001$). Although the serum melatonin levels at two different time points during night sleep were lower in PD patients than the controls, these differences did not reach statistical significance ($p = 0.104$ at 00:00 am, $p = 0.528$ at 05:00 am). There was no significant correlation between the PSQI scores and serum melatonin levels in patient group ($p > 0.05$). However, there was a significant but weak correlation ($r = -0.353$, $p = 0.025$) between ESS scores and the serum melatonin levels measured at 05:00 hours in patients, but not between the melatonin levels measured at 00:00 hours.

Conclusion: Sleep evaluation questionnaires such as, PSQI and ESS, can provide useful information in PD patients with mild sleep disturbances. However, serum melatonin levels alone were not helpful in diagnosing the sleep disorders.

Keywords: Parkinson's disease, melatonin, Pittsburg Sleep Quality Index, Epworth Sleepiness Scale, sleep disorders

ÖZ

Amaç: İdiyopatik Parkinson hastalığında (PH), uykuyu başlatmakta zorluk, uyku süresinde kısalma, sık uyanma ve artmış gündüz uykululuğu gibi uyku bozuklukları en sık görülen non-motor semptomlar arasındadır. Ancak, hastalar genellikle bu yakınmaları motor şikayetleri kadar önemli görmez ve dile getirmezler. Bu çalışmada Parkinson hastalarındaki gizli uyku bozukluklarının uyku değerlendirme ölçekleri kullanılarak araştırılması ve bu testler ile gece uykusu sırasında bakılan serum melatonin düzeyleri arasındaki ilişkinin incelenmesi amaçlanmıştır.

Yöntem: Hareket hastalıkları polikliniğinde kayıtlı, 50 yaşın üstündeki toplam 40 (19, kadın) Parkinson hastası ile yaş ve cinsiyet açısından benzer, 40 sağlıklı kontrol bireyi (20, kadın) çalışmaya dahil edilmiştir. Tüm bireyler Pittsburg Uyku Kalitesi İndeksi (PUKİ) ve Epworth Uykululuk Ölçeği (EUÖ) ile değerlendirilmiştir. Tüm bireylerden gece uykusu sırasında 00:00 ve 05:00'te iki kez kan örneği alınarak serum melatonin düzeyleri ölçülmüştür. İki grup, demografik veriler, uyku değerlendirme ölçekleri ve serum melatonin düzeyleri açısından karşılaştırılmıştır.

Bulgular: Parkinson hastalarının PUKİ ve EUÖ puanları, kontrol bireylerine kıyasla anlamlı derecede yüksek saptanmıştır ($p < 0.001$). Her ne kadar Parkinson hastalarında gece iki farklı saatte bakılan serum melatonin düzeyleri kontrollere göre daha düşük bulunmuş olsa da, bu farklılıklar istatistiksel anlamlılığa ulaşmamıştır. Hasta grubunda, PUKİ puanları ile serum melatonin düzeyleri arasında bir ilişki saptanmamıştır ($p > 0.05$). Öte yandan, hastaların EUÖ puanları ile 00:00'da değil ama 05:00'te ölçülen serum melatonin düzeyleri arasında anlamlı fakat zayıf bir ilişki ($r = -0.353$, $p = 0.025$) bulunmuştur.

Sonuç: Parkinson hastalarındaki gizli kalmış uyku bozukluklarının tanısında PUKİ ve EUÖ gibi uyku değerlendirme ölçekleri faydalı olabilir; ancak, serum melatonin düzeyleri tek başına yeterli değildir.

Anahtar Kelimeler: Parkinson hastalığı, melatonin, Pittsburg Uyku Kalitesi İndeksi, Epworth Uykululuk Ölçeği, uyku bozuklukları

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INTRODUCTION

Sleep disturbances such as, difficulty in initiation of sleep, decrease in total sleep duration and efficacy, frequent awakenings, and increased daytime sleepiness are listed among the most common non-motor symptoms in patients with idiopathic Parkinson's disease (PD), and the incidence has been reported within a wide range of 42–98% in different case series (1–5). In general, these PD-related disturbances are not classified within primary sleep disorders such as, sleep apnea syndrome. The pathogenic mechanisms include the primary degeneration of locus coeruleus, which regulates sleep process, and the change in levels of non-dopaminergic neurotransmitters due to the degenerating nature of the disease affecting various neurological systems (6). Several other factors such as, the main motor symptoms in PD (e.g. tremor and rigidity) and dopaminergic therapies can also precipitate the sleep disturbances (1, 7).

The widely accepted mechanism in sleep regulation is the involvement of several different centers or a system connected with a complicated neural web, stimulating or inhibiting each other using various neurotransmitters and hormones, rather than a single group of neurons controlling the sleep stages (8). The sleep-wake pattern, namely circadian system, is under the control of hypothalamic suprachiasmatic nucleus that controls the pineal gland, which regulates the melatonin secretion (9). Pinealocytes are light sensitive cells that are responsible for melatonin secretion. Bright light inhibits melatonin secretion from these cells. Melatonin secretion increases at night and dark areas because this inhibition is removed. Melatonin secretion is in circadian rhythm, increases in 9.00–10.00 pm and had its maximum level at night 11.00 pm – 05.00 am (10).

Melatonin, a sleep hormone, is mainly associated with the initiation of sleep, latent period and efficacy, rather than the total time of sleep. These have been attributed to its hypothermic effects and role in thermoregulation of the body (8, 9). Many neurodegenerative disorders have been associated with sleep disturbances due to the changes in the pattern of melatonin secretion. Initial studies comparing untreated to treated PD patients with or without motor complications demonstrated higher melatonin secretion in treated patients compared to untreated controls. Later studies have demonstrated that PD patients have a decreased melatonin secretion compared to the controls. Despite the extensive data on serial measurements of melatonin levels, its role in patients with PD is unclear (7, 9, 11–13). Alterations in patterns of melatonin secretion may contribute to the underlying pathophysiology of these disorders. Antioxidant effect of melatonin has been demonstrated *in vivo* models to protect against oxidative stress, and can protect against 1-methyl 4-phenyl 1-, 2-, 3-, 6-tetrahydropyridine (MPTP) induced neurotoxicity in experimental models of PD (14, 15).

Sleep disturbances lead to extensive daytime sleepiness, which adversely affects the quality of life. However, the majority of PD patients do not complain of sleep disturbances, mainly for two reasons: either they do not consider these symptoms as important as their motor symptoms, or they do not consider these symptoms in relation with PD. Thus, it is important to question the quality of sleep and its modalities and examine the patient using sleep evaluation scales during the clinical practice.

The aim of this study was to investigate the PD patients using sleep evaluation scales for mild sleep disturbances, and to evaluate the relationship between these tests and the serum levels of melatonin during night-sleep.

METHODS

Study Population

Patients older than 50 years, diagnosed with PD and registered in "Movement Disorders Out-patient Clinic" were screened. Clinical

diagnosis of the PD was made according to the criteria of UK Parkinson's Disease Society Brain Bank (16). Clinical staging of PD was made with Unified Parkinson's Disease Clinical Rating Scale (UPDRS) and Hoehn-Yahr Scale (17, 18). All patients were assessed using the criteria for the diagnosis of probable and possible PD-dementia and Beck Depression Scale (19, 20).

Participants with the diagnosis of primary sleep disorders (including restless legs syndrome), dementia, depression, psychosis, neuropathic pain, malignancy, any other neurological, or systemic (e.g., pulmonary, endocrine, rheumatologic etc.) disease were excluded. Also, subjects who were using alcohol, psychiatric (e.g., anti-depressants, anti-psychotics etc.), sedative or stimulant drugs, and who has excessive consumption (i.e., more than 2 cups a day) of beverages containing caffeine or similar substances were not included in the study.

A total of forty consecutive patients (19, female) between the ages 51 and 81 were included in the study. Control group consisted of 40 healthy, age and sex-matched control subjects (20, female) who were eligible for the study criteria. All participants underwent a thorough systemic and neurological examination.

Patients with PD were on following decent medications: 5 patients were using levodopa only, 5 patients dopamine-agonists only, 1 patient rasagiline only, 12 patients combination of levodopa and dopamine agonists, 7 patients combination of rasagiline and dopamine agonists, 6 patients combination of levodopa, dopamine agonists and rasagiline, 4 patients were taking combination of levodopa, dopamine agonists, rasagiline and amantadine.

The study protocol was in accordance with the Helsinki Declaration of Human Rights, and was approved by Tepecik Education and Research Hospital Committee for Research Ethics and all subjects gave written informed consent to participate in the study.

Sleep Evaluation Scales

All subjects were assessed using validated Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scales (ESS) (21, 22). Scores above 5 in PSQI, and scores above 10 in ESS were defined as sleep disturbance (21, 22).

Serum Levels of Melatonin

All subjects were hospitalized for one night in a single, semi-illuminated (with dimmed red light) room with lightproof curtains. Intravenous catheters were placed in antebrachial veins in order not to awake the subjects during blood sampling. Patients were given the last PD medications not later than 6:00 pm and asked to sleep at their routine bedtime. Blood samples were taken twice in every subject at 00:00 and 05:00 hours. Blood samples were immediately stored at 4°C for 15 minutes, centrifuged at 2000 rpm for 10 minutes and the extracted serum was stored at -86°C, at dark until assayed. Serum levels of melatonin were detected by using commercially available human-melatonin (MT)-ELISA kits (Sunred Biological Technology, Shanghai, PRC) according to the manufacturers' instructions (Serial no: 201-12-1014).

Statistical Analysis

Statistical analyses were performed using SPSS v.15.0 for Windows (Statistical Package for Social Sciences, SPSS, Inc., Chicago, IL). Categorical variables were compared using χ^2 -test. Continuous variables were tested using Kolmogorov-Smirnov normality test. Variables with normal distribution were compared using Student's t-test, other variables were compared using Mann-Whitney U test. Correlation analyses were performed using Spearman correlation analysis; p values <0.05 were considered as significant.

RESULTS

Demographical and clinical features of patients with PD are summarized in Table 1. Patient and control groups were similar according to age ($p=0.107$) and gender ($p=0.823$). UPDRS scores of patients varied between 4 and 67. Hoehn-Yahr scores varied between 1 and 4.

According to PSQI, 28 patients (70.0%) had higher scores than the cut-off value of 5, whereas 8 control subjects (20.0%) had scores higher than 5 ($p<0.001$). The comparison of patients with PD and controls according to the sleep scales and serum levels of melatonin at two different time points are summarized in Table 2. Patients with PD had significantly higher scores in sleep evaluation tests.

According to ESS, 7 patients (17.5%) had higher scores than the cut-off value of 10, however, none of the controls had such a high score to indicate a sleep disturbance ($p=0.006$). Patients had significantly higher scores than the controls (Table 2).

Although, the serum levels of melatonin at two different time points during night-sleep were lower than the controls, this difference did not reach statistical significance (Table 2).

The correlation analysis between the serum levels of melatonin and duration of disease ($p=0.216$, $r=0.600$), UPDRS scores ($p=0.264$, $r=0.792$), or Hoehn-Yahr scores ($p=0.190$, $r=0.656$) did not reveal any significant results in PD patients.

Table 3 lists the correlation analysis between the sleep evaluation scales and serum melatonin levels in PD patients and controls. No significant correlation between the PSQI scores and serum levels of melatonin was found in the patient group. However, there was a significant but weak correlation ($r=-0.353$, $p=0.025$) between ESS scores and the serum melatonin levels measured at 05:00 hours in the patient group, but not between the serum levels of melatonin measured at 00:00 hours.

DISCUSSION

In PD, sleep disturbances usually begin simultaneously with motor symptoms of the disease, but might also precede, in rare instances. Nocturnal awakening and sleep fragmentation are the most common disturbances, which are the major factors leading to excessive daytime sleepiness (23). The mechanism beneath the sleep disturbances in PD is unclear, as is the case in the Alzheimer's disease (24). Since PD is diagnosed usually in the elderly who also have co-morbid factors affecting the sleep, it is difficult to clarify the pathophysiology.

In this study, PSQI and ESS were used to evaluate the sleep disturbances and daytime sleepiness, since these tests have been previously validated in Turkish patients (21, 22). Polysomnography (PSG) is the gold standard in the diagnosis of sleep disturbances. However, readily available sleep scales are more commonly used in clinical practice for the evaluation of sleep disturbances. PSQI and ESS are such practical tests to apply. However, in 2002, Chaudhuri et al. (25) suggesting that PSQI could be insufficient in PD, which was initially developed for general population, not specifically for PD patients, developed another sleep scale (Parkinson's disease sleep scale, PDSS) to assess sleep and nocturnal disability in PD patients. Later, in 2009, Uemura et al. (26) compared the reliability of PDSS, PSQI, ESS, and PSG in PD patients, and reported a significant correlation between PDSS and PSQI and ESS scores. In 2014, Schrempf et al. (24) recommended PSQI for the evaluation of sleep disturbances and ESS for the evaluation of daytime sleepiness, as these scales were validated for patients with PD.

The scores of PSQI and ESS were significantly higher in patients with PD, indicating the sleep disturbances. The frequency of sleep disturbances was 70% in PD vs. 8% in controls. In clinical practice, the high frequency of sleep disturbances in patients without overt sleep complaints could be partially explained by the fact that, patients usually complain of motor symptoms, but sleep disturbances are usually revealed by questioning.

Table 1. Demographical and clinical features of patients with Parkinson's disease (PD) and controls

	Controls (n=40)	Total (n=40)	PD Female (n=19)	Male (n=21)
Age* (years)	65.38±8.28	68.32±7.92	66.21±8.34	70.24±7.18
UPDRS Scores*	N/A	33.10±17.56	34.79±18.74	31.57±16.73
Hoehn-Yahr Scores*	N/A	2.14±1.08	2.26±1.17	2.02±1.01
Disease duration* (years)	N/A	8.23±5.86	9.21±6.70	7.33±4.98
Disease duration <10 years (n, %)	N/A	25 (62.5)	12 (48.0)	13 (52.0)
Disease duration >10 years (n, %)	N/A	15 (37.5)	7 (46.7)	8 (53.3)

* Data expressed as mean ± standard deviation.

PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Clinical Rating Scale.

N/A, not applicable.

Table 2. Comparison of patients with PD and controls according to the sleep scales and serum levels of melatonin, expressed as mean ±1 standard deviation.

	PD	Controls	P-value
Sleep Evaluation Scales			
PSQI score	7.25±3.36	3.35±2.11	<0.001
ESS score	6.68±5.26	2.28±2.65	<0.001
Serum Melatonin Levels (pg/ml)			
At 00.00 am	16.16±16.87	21.28±21.89	0.104
At 05.00 am	15.49±15.05	19.43±29.54	0.528

PD, Parkinson's disease; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

bold indicates significance value <0.05.

In addition, daytime sleepiness was found in 17.5% of patients vs. none of the controls. This data suggests that excessive daytime sleepiness is not solely related to sleep disturbances. Previously, fragmentation of night sleep was believed to be the reason of daytime sleepiness; however, Roth et al. (27), related the disturbed circadian rhythm, degeneration in central nervous system and the medications used in daytime to excessive daytime sleepiness. In one study, the frequency of daytime sleepiness was reported as 15.5% in PD, 4% in controls with diabetes mellitus, and 1% in healthy controls (28). This data was later supported by several other studies (24, 25).

Circadian rhythm is a physiological and behavioral cycle lasting approximately for 24 hours and is regulated by suprachiasmatic nucleus (SCN) in anterior hypothalamus. Sunlight is the major environmental

Table 3. The correlation analysis between the sleep scales and serum melatonin levels in PD patients and controls.

	PD (n=40)				Controls (n=40)			
	Melatonin at 00:00 am		Melatonin at 05:00 am		Melatonin at 00:00 am		Melatonin at 05:00 am	
	r	p	r	p	r	p	r	p
PSQI	-0.087	0.592	-0.099	0.544	-0.026	0.873	-0.157	0.355
ESS	-0.127	0.435	-0.353	0.025	-0.056	0.730	-0.076	0.641

PD, Parkinson's disease; PSQI, Pittsburg Sleep Quality Index; ESS, Epworth Sleepiness Scale.

r, rho-correlation coefficient; p, significance value.

bold indicates significance value <0.05.

factor affecting this system (29). Although there are several other hormones and neurotransmitters that function in sleep regulation, melatonin is the major hormone secreted by pineal gland under the control of SCN that affects sleep. Levels of melatonin increases in dark, and peak between 02.00 and 04.00 hours. In patients with PD, a slight shift in melatonin peak occurs, by the effect of advanced age and dopaminergic medications, shifting the peak until 06.00 am (1, 11). For this reason, the sampling time for the measurement of serum melatonin levels were set as 00.00 and 05.00 hours. Although, the serum levels of melatonin were higher at 00.00 am than 05.00 am in both the patients and the controls, there was no significant difference between the patients and controls. This data also suggested the absence of the shift (or minimal) in peak levels, which was mentioned in previous studies (1, 11). The lack of significant difference in serum levels of melatonin in PD patients who were all receiving dopaminergic medications and healthy controls might support the data of Bolitho et al. (9), besides other studies suggesting a decrease in PD patients compared to controls (12).

Levels of melatonin decrease with aging. In older patients with PD, melatonin levels increase with the effect of dopaminergic therapy, similar to the levels of healthy age-matched controls. In spite of the initial studies with exogenous melatonin given to older patients with PD showed no effect of melatonin on sleep regulation, later studies demonstrated the neural suppression and sleep promoting effects of melatonin (1, 9, 30, 31). All participants in the present study were older than 50 years and all patients were on decent dopaminergic medications. This was explained by the fact that all patients were receiving dopaminergic therapy.

The limitations of this study include the low number of study participants and the patient group was not homogeneous for disease characteristics. During the inclusion of the patients, we aimed to select PD patients who have no any sleep complaints, so the duration of illness and dopaminergic drug levels could not be standardized. Due to the low number of patients, subgroup analyses are not done. The lack of analysis of circadian rhythm tests is another limitation of the study. Since we could not get reliable information about circadian rhythm regarding the pre-illness period, this data was not included in the study.

In conclusion, PSQI and ESS are valuable tools in the clinical assessment of mild sleep disturbances in patients with PD. However, serum melatonin levels, alone, were not helpful in diagnosing the sleep disorders.

Ethics Committee Approval: The study protocol was in accordance with the Helsinki Declaration of Human Rights, and was approved by Tepecik Education and Research Hospital Committee for Research Ethics.

Informed Consent: All participants gave written informed consent to participate in the study.

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