



Sleep Quality and Cognitive Impairment in Patients with Parkinson's Disease in Iran

İran'da Parkinson Hastalarında Uyku Kalitesi ve Kognitif Bozukluk

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Summary

Objective: To evaluate the cognitive status and sleep quality and their association in patients with Parkinson's disease (PD).

Materials and Methods: In this analytical cross-sectional study, 120 patients with PD were selected from 22-Bahman and 17-Shahrivar hospitals. Demographic information was recorded on a form and Parkinson's severity was determined using the Hoehn and Yahr scale (HY). Pittsburgh Sleep Quality Index (PSQI) and Epworth sleepiness scale (ESS) were used for the assessment of sleep quality and excessive daytime sleepiness, respectively. Cognitive status was assessed using the Montreal Cognitive Assessment questionnaire.

Results: The mean age of patients with PD was 65.9±11.7 years, and 67.5% were men. Cognitive impairment was found in 113 (94.2%) patients, poor sleep quality in 87 (72.5%), and excessive daytime sleepiness in 27 (22.5%) patients. The mean PSQI and ESS scores were 9.03±4.70 and 7.38±3.73, respectively. There was a significant association between cognitive status and sleep quality, as well as daytime sleepiness (independent sample t-test, p<0.0001 for both).

Conclusion: There is a significant association between cognitive impairment and poor sleep quality as well as excessive daytime sleepiness.

Keywords: Cognitive disorders, Parkinson's disease, sleep disorders

Öz

Amaç: Parkinson hastalığı (PH) olan hastalarda, bilişsel durum ve uyku kalitesi ve bunların birlikteliğini değerlendirmektir.

Gereç ve Yöntem: Bu analitik kesitsel çalışmada, PH olan 120 hasta, 22-Bahman ve 17-Shahrivar hastanelerinden seçildi. Demografik bilgi formu dolduruldu ve Parkinson şiddeti Hoehn ve Yahr (HY) ölçeği kullanılarak belirlendi. Pittsburgh Uyku Kalitesi İndeksi (PUKİ) ve Epworth uyku kalitesi skolası (ESS), sırasıyla uyku kalitesini ve gündüz aşırı uykululuğun değerlendirilmesi için kullanılmıştır. Bilişsel durum Montreal Bilişsel Değerlendirme anket formu kullanılarak değerlendirildi.

Bulgular: PH hastalarının yaş ortalaması 65,9±11,7 yıl idi ve bunların %67,5'i erkekti. Hastaların 27'sinde (%22,5) kognitif bozukluk, 87'sinde (%72,5) gündüz aşırı uykululuk ve 113'ünde (%94,2) kötü uyku kalitesi bulundu. PUKİ ortalama ve ESS skorları sırasıyla 9,03±4,70 ve 3,73±3,73 idi. Kognitif durum ve uyku kalitesi yanı sıra gündüz uykululuk arasında bir anlamlı ilişki saptandı (p<0,0001).

Sonuç: Kognitif bozukluk ve kötü uyku kalitesi yanı sıra gündüz aşırı uykululuk arasında anlamlı bir ilişki vardır.

Anahtar Kelimeler: Kognitif bozukluklar, Parkinson hastalığı, uyku bozuklukları

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and a common movement disorder, which primarily affects the substantia nigra. PD is a chronic progressive disease that is pathologically characterized by degeneration of dopamine-producing neurons in the substantia nigra, formation of Lewy bodies, and neuronal death. Clinical presentations of PD include resting tremor, bradykinesia, rigidity, postural instability, and abnormal gait (1).

Sleep disorders are one of the most common non-motor symptoms in PD, which reduce the patients' quality of life (2,3,4). The prevalence of sleep disorders in patients with PD is estimated as 65-95% (5,6,7,8), which increases with disease progression (9).

Cognitive impairment and dementia is another common and disabling non-motor symptoms in PD that affects patients' daily functioning (10). The prevalence of cognitive impairment has been reported from 14.8% to 42.5% (11,12,13). Studies have demonstrated that 75% of patients with PD can progress to dementia. Cognitive decline can affect prognosis, nursing home placement, and mortality rates in patients with PD (14). The underlying mechanisms of cognitive impairment in PD are not known.

It is important to know the association of sleep disturbances and cognitive function to diagnose early and treat cognitive impairment, and prevent reduction or improve quality of life of patients with PD because cognitive impairment and sleep disturbances contribute to poor outcomes and quality of life in these patients. This study aimed to investigate the quality of sleep and cognitive status in patients with PD, as well as the association between cognitive status and sleep disorders in PD because there is a correlation between the pathophysiologic mechanism of sleep disturbances and cognitive impairment in PD (15), and there is no information regarding these disorders in patients with PD in Iran.

Materials and Methods

This cross-sectional study was conducted on patients with PD who were referred to neurology clinic at 22-Bahman and 17-Shahrivar hospitals, Mashhad, Iran from October 2013 to Jun 2014. Eligible patients were selected using the convenient sampling method. PD diagnosis was made clinically based on the United Kingdom Parkinson's Disease Society Brain Bank criteria (16) and the disease severity was determined using the Hoehn and Yahr (HY) scale (17). Patients with probable diagnosis of Parkinson's disease, those with dementia, and those taking sedative drugs were excluded from the study. The study protocol was approved by Institutional Review Board at Mashhad Branch, Islamic Azad University, and all patients gave informed written consent before enrollment.

Eligible patients were selected using the non-probability consecutive sampling method, which usually selects patients based on their accessibility, or by the personal judgment of the researcher. In total, 120 patients with PD were included in the final analysis.

Sleep disorders including insomnia, hallucinations, daytime sleepiness, restless leg syndrome, and nightmares were evaluated using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) questionnaires. Cognitive disorders

were assessed based on the Montreal Cognitive Assessment (MoCA) questionnaire. PSQI and ESS questionnaires were self-administered but the MoCA questionnaire was completed by a trained interviewer.

The PSQI is a self-administered questionnaire for the assessment of sleep quality and disturbances over one month. It has 19 individual items that generate seven composite scores for subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The global score is obtained through the sum of the scores of these seven components. A global PSQI score greater than 5 indicates poor quality of sleep (18). The reliability and validity of the Persian version of PSQI was approved in Iran with a Cronbach's alpha coefficient of 0.77 (19).

ESS is a self-administrated questionnaire with 8 questions that evaluates the level of daytime sleepiness. A score of 10 or greater indicates excessive daytime sleepiness (20). The validity and reliability of Persian version of ESS has been approved in an Iranian study (21).

MoCA is a rapid screening instrument for the detection of cognitive impairment. It is a 30-point test for the evaluation of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A score of 26 or less indicates cognitive impairment (22). The Persian version of MoCA was used in Iran and its validity and reliability was approved with a Cronbach's alpha of 0.77 (23).

Based on the mentioned methods, patients were diagnosed as having cognitive impairment if they scored 26 or less in MoCA, daytime sleepiness if they scored 10 or more in the ESS, and as having poor sleep quality if a score of more than 5 was recorded in the PSQI.

Statistical Analysis

Data analysis was performed using SPSS version 22.00 and Statistica version 10.0 for Windows. Data are presented as mean and standard deviation (SD) for quantitative data and number and percentage for categorical data. Spearman's correlation test was used to find a correlation between cognitive impairment and sleep disorder. The chi-square test was used to compare categorical data between groups, and the independent sample t-test or Mann-Whitney U test were used for the comparison of quantitative data as appropriate. The multiple logistic regression model was used to remove confounding factors from the relationship between sleep quality and cognitive impairment. A p value less than 0.05 was considered as significant.

Results

A total number of 120 patients with PD without dementia were evaluated. The mean age of the patients was 65.9 ± 11.7 years (range, 38-86 years) and 60% were aged 65 years or more. Among the patients, 81 (67.5%) were men and 39 (32.5%) were women. Ninety-one patients (75.8%) were taking levodopa alone or in combination with other drugs, and seven patients (5.8%) were taking drugs other than levodopa.

Five (4.2%) of the 120 patients with PD had a history of hospitalization due to medication control and 44 patients (36.7%)

had a history of hospitalization due to a general medical condition. The mean duration of PD was 2.6±2.7 years. The duration of disease in most patients (n=31; 25.8%) was less than one year. Based on the Hoehn and Yahr (HY) scale, the majority (n=90; 75%) of patients were at stage I or II of PD, 13 (10.8%) patients were stage III, 14 (11.7%) patients were stage IV, and three (2.5%) patients were at stage V.

Cognitive impairment was found in 113 (94.2%) patients with PD, poor sleep quality in 87 (72.5%), and excessive daytime sleepiness in 27 patients (22.5%) [9.2% (n=11) with ESS score 10-12, and 13.3% (n=16) with ESS score 12-24]. Cognitive impairment was observed in 100% of patients with poor sleep quality and excessive daytime sleepiness. ESS ≥10 was found in 23.9% of patients with cognitive impairment, and PSQI >5 was found in 77% of our patients with PD and cognitive impairment.

There was no significant difference in sleep disorder and daytime sleepiness between men and women with PD (Table 1), whereas cognitive impairment was significantly higher in men than in women with PD (p=0.02) (Table 1).

Mean PSQI, ESS, and MoCA scores in patients with PD were 9.03±4.70, 7.38±3.73, and 17.38±5.20, respectively. Patients with PD and cognitive impairment had significantly poorer sleep quality and more daytime sleepiness than those without cognitive impairment (PSQI score: 9.32±4.69 vs. 4.43±0.53, p<0.0001; ESS score: 7.77±3.50 vs. 1.14±0.69, p<0.0001). In addition, there was a significant direct correlation between disease duration and severity of PD (r=0.60, p<0.0001). The mean PSQI was not significantly different between men and women but there was a significant difference in mean MoCA and ESS scores between the sexes (Table 1). There was a significant inverse correlation between MoCA and PSQI score as well as ESS (r=-0.22, p=0.01 for PSQI and r=-0.51, p<0.0001 for ESS) (Figure 1, 2). No significant correlation was observed between MoCA and PSQI scores in men and women separately (r=-0.20, p=0.06 for men and r=-0.24, p=0.13 for women). There was a significant inverse correlation

between MoCA and ESS scores in men and women separately (r=-0.52, p<0.001 for men and r=-0.43, p=0.007 for women), and this inverse correlation was stronger in men than in women (Figures 3a, b). Also, the inverse correlation between MoCA and ESS scores was stronger in patients with PD aged <65 years than in those aged ≥65 years (r=-0.68, p<0.001 and r=-0.41, p<0.001, respectively).

A significant association was found between severity of PD and cognitive impairment, as well as poor sleep quality and daytime sleepiness (p=0.034, p=0.006 and p<0.001, respectively). There

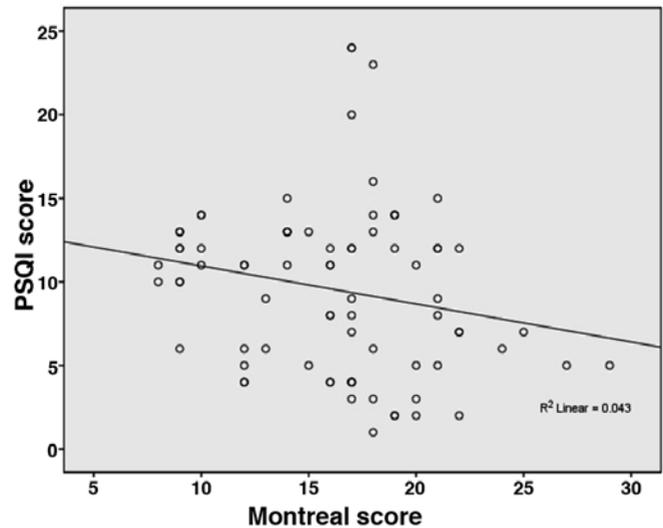


Figure 1. Relationship between cognitive statuses and sleep disturbances based on Pittsburgh Sleep Quality Index score in patients with Parkinson's disease

PSQI: Pittsburgh Sleep Quality Index

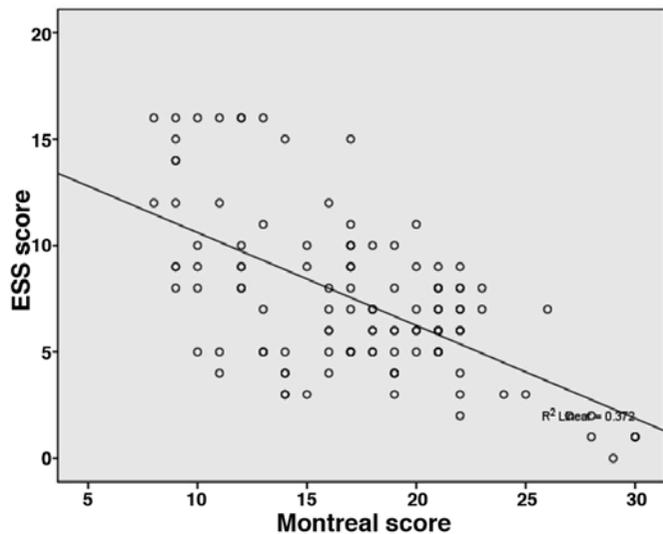


Figure 2. Relationships between cognitive statuses and sleep disturbances based on Epworth Sleepiness Scale, score in patients with Parkinson's disease

ESS: Epworth Sleepiness Scale

Table 1. Sleep quality and cognitive status in Parkinson's disease patients according to the gender			
Parameter	Men	Women	p value (95% CI)
PSQI score (mean±SD)	9.54±5.01	7.97±3.82	0.06 (-0.74-3.21)
ESS score (mean±SD)	7.89±3.86	6.29±3.27	0.03 (0.16-3.03)*
MoCA score (mean±SD)	16.20±4.59	19.85±5.59	<0.0001 (-5.55-1.74)*
Poor sleep quality, n (%)	59 (72.8)	28 (71.8)	0.90
Daytime sleepiness, n (%)	20 (24.7)	7 (18.4)	0.44
Cognitive impairment, n (%)	79 (97.5)	34 (87.2)	0.02*

Cognitive impairment: Mild cognitive impairment, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, MoCA: Montreal cognitive assessment, CI: Confidence interval, *p<0.05 significant

was no significant association between disease duration and cognitive impairment or poor sleep quality or daily sleepiness ($p=0.69$, $p=0.34$ and $p=0.14$, respectively), whereas a significant direct correlation was found between the duration of PD and ESS score ($r=0.21$, $p=0.019$). There was no significant association between drug used and cognitive impairment, poor sleep quality or daytime sleepiness ($p=0.44$, $p=0.08$, and $p=0.43$, respectively).

Multiple logistic regression analysis was used and the association between cognitive impairment and sleep quality was adjusted for age, sex, duration and severity of disease, and type of treatment. After adjustment for confounders, the relationship between cognitive impairment and poor sleep quality or daytime sleepiness changed to non-significant ($p=0.99$ and 0.76 , respectively), and only age remained in the model. However, the raw PSQI score predicted cognitive impairment in patients with PD with an odds ratio of 2.14 [95% CI: (1.03-4.44); $p=0.41$]. Therefore, poor sleep quality or disturbances were not predictors of cognitive impairment.

Discussion

This study results showed no significant association between poor sleep quality and cognitive impairment in patients with PD after removing confounding factors. Although the frequency of cognitive impairment in patients with PD was 94.2%, and it was observed in all patients with poor sleep quality and excessive daytime sleepiness, there was a weak correlation between MoCA and PSQI scores, as well as the ESS score.

The weak correlation between MoCA and PSQI in our study may be attributed to the fact that PSQI cannot evaluate PD-related nocturnal symptoms. In addition, poor sleep quality may be associated with aging rather than PD itself, as it was shown in the multiple logistic regression analysis results after adjusting for age and other confounding factors, which was unable to find a significant association between cognitive impairment and poor sleep quality.

In most of previous studies, both abroad and within Iran, sleep or cognitive disorders have always been investigated in patients with PD separately (24,25,26,27,28), and our study is the first in our country to evaluate the relationship between sleep quality and cognitive status in patients with PD.

Recently, in a case-control study, Najafi et al. (27) evaluated sleep quality in 34 patients with PD in Isfahan, Iran, using the PD sleep scale. They showed poorer nocturnal sleep quality in patients with PD than in the control group. They found no significant correlation between sleep quality and duration of the disease. These findings are similar to ours but they did not report the rate of poor sleep quality, which we have reported (27). Another cross-sectional study in Tehran, Iran, investigated cognitive impairment in 87 patients with PD using the Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-Cog). That study showed an inverse correlation between age and memory, as well as learning. Also, a direct correlation was found between education level and attention, memory, learning, executive function, and visuospatial function. The authors did not report the rate of cognitive impairment in patients with PD or the mean score of SCOPA-Cog (28).

Yarnall et al. (25), in a case-control study, evaluated cognitive impairment in 219 patients whose PD was newly-diagnosed using Mini-mental state examination (MMSE) and MoCA questionnaires. They found cognitive impairment in 42.5% of patients at 1.5 SD below normative values. Also, patients with PD had lower MMSE and MoCA scores than the control group.

Videnovic et al. (29), used MoCA, ESS and PSQI questionnaires and found excessive daytime sleepiness in 60% of PD patients versus 27% in control group. Mean ESS score in PD patients was higher than the control group while the PSQI score was not significantly different between the two groups. Goldman et al. (30) evaluated the association between daytime sleepiness and impaired sleep quality and cognitive impairment by applying PSQI and ESS. Cognitive impairment was identified in 43% of patients, poor sleep quality in 59.1%, and excessive daytime sleepiness in 49.5% of patients. The rate of cognitive impairment and sleep

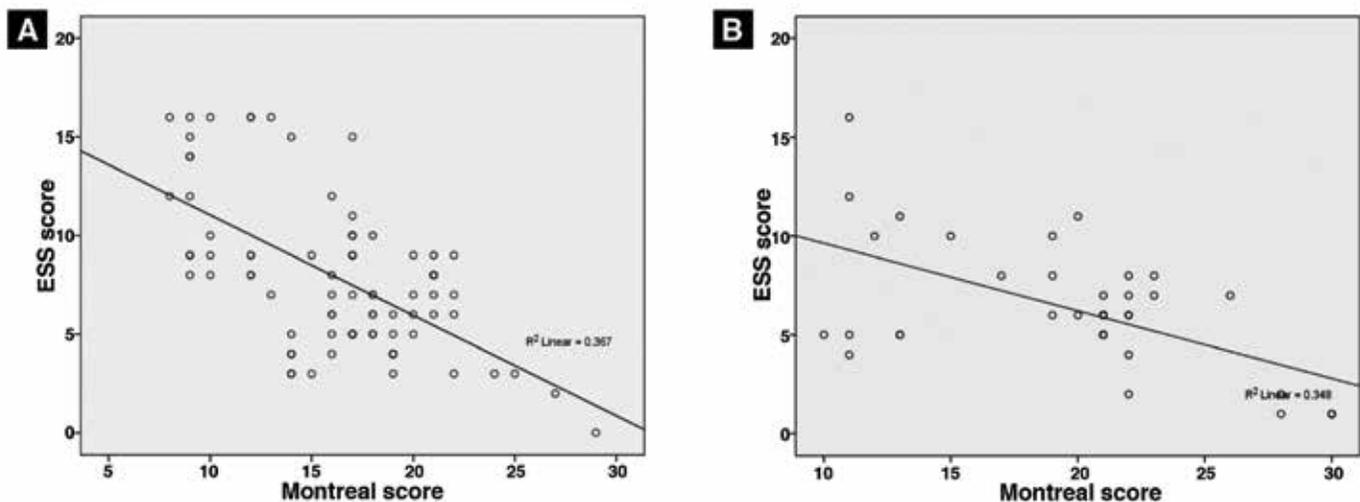


Figure 3. Relationships between Montreal cognitive assessment and Epworth Sleepiness Scale scores in men (A) and women (B) with Parkinson's disease
ESS: Epworth Sleepiness Scale

disorders in our study was higher, whereas the rate of excessive daytime sleepiness was lower in our study than in Goldman et al.'s (30) study. They found ESS ≥ 10 in 45% of patients with cognitive impairment, whereas it was found in 23.9% of patients with cognitive impairment in our study. In the Goldman et al. (30) study, PSQI > 5 was found in 60% of those with cognitive impairment, and we found the same result in 77% of our patients PD and cognitive impairment. In contrast to our results, Goldman et al. (30) found a significant association of excessive daytime sleepiness and cognitive impairment in patients with PD.

Yu et al. (24) evaluated sleep disorder in 211 patients with PD using the PSQI and found poor sleep quality in 64.5% of patients, which was lower than our finding (72.5%). A recent study that included early, untreated patients with PD failed to find any difference in changes in sleepiness and sleep structure using polysomnography between the PD and control group, with the exception of significantly increased rapid eye movement sleep without atonia observed in PD group, which cannot be compared to our results because we did not include control group in our study (31). Contrary to the present study results, the recent study by Kim et al. (32), which assessed the relationship between sleep disturbances and cognitive impairment using PDSS, PSQI, ESS, interstimulus intervals, MMSE and MoCA, failed to show a correlation of MoCA/MMSE with PSQI or ESS, but did find a significant correlation of MoCA/MMSE with sub-items of PDSS, PD-related sleep disturbances.

Our study findings did not confirm the results of previous studies regarding the association between daytime sleepiness and cognitive impairment (30). In our study, after adjustment for confounding factors, this association changed to non-significant. This may be due to the confounding effect of age on cognitive status, because age was the only variable that remained in the model, but its association with cognitive impairment was not significant ($p=0.06$) and not reaching significance level may be due to the small sample size. However, the rate of cognitive impairment in our study (94.2%) was higher than in previous studies, although the majority of our patients with PD were stage I or II. Such a high rate of cognitive impairment has not been reported until now (27,28,29). We found no explanation for this high rate of cognitive impairment in primary stages of PD in our patients. This may be explained by pathophysiologic mechanisms involved in this process. The possible pathophysiologic correlations between cognitive impairment and sleep disturbance and excessive daytime sleepiness in PD may be explained by the involvement of the medulla and pons prior to the midbrain based on the Braak staging hypothesis (15).

The lack of an age-matched healthy control group is the main limitation of the present study. In addition, although PSQI has been recommended for use in patients with PD, it does not include PD-related non-motor or motor symptoms during the night, which limits the clinical significance of our study. Lack of separate analysis of PSQI components is another limitation of the study.

Further case-control and cohort studies using different diagnostic tools are required to confirm our findings regarding the relationship between sleep disturbances and cognitive impairment. Also, the etiology of such high cognitive impairment in our patients with PD should be investigated in future studies.

Conclusion

In conclusion, the study findings showed that cognitive impairment is present in all patients with PD who have poor sleep quality or excessive daytime sleepiness. However, sleep quality or disturbances were not predictors of cognitive impairment after removing confounding factors and this association was more attributed to age. Therefore, poor sleep quality or daytime sleepiness are not useful factors to predict cognitive impairment in patients with PD.

Ethics

Ethics Committee Approval: The study protocol was approved by Institutional Review Board at Mashhad Branch, Islamic Azad University, Informed Consent: All patients gave informed written consent before enrollment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Seyed Mebran Homam, Concept: Seyed Mebran Homam, Design: Seyed Mebran Homam, Data Collection or Processing: Narges Sahebzadeh, Morteza Mazloum Farsi Baf, Analysis or Interpretation: Narges Sahebzadeh, Literature Search: Narges Sahebzadeh, Morteza Mazloum Farsi Baf, Writing: Narges Sahebzadeh, Morteza Mazloum Farsi Baf.

Conflict of Interest: No conflict of interest was declared by the authors.

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