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Depression and Sleep Quality in Restless Legs Syndrome/Willis-Ekbom Disease

Huzursuz Bacak Sendromunda Depresyon ve Uyku Kalitesi

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ABSTRACT

Objectives: Restless legs syndrome (RLS)/Willis-Ekbom disease (WED) is a well-known neurological sensory motor disorder. As a result of sleep fragmentation, quality of life has effected and incidence of anxiety and depression increase. Our aim with this study is to obtain the effects of RLS/WED on sleep quality and psychiatric well-being and their relationship with disease severity.

Methods: In total, 122 RLS/WED was diagnosed with RLS/WED according to the International RLS Study Group (IRLSSG) diagnostic criteria. All partipicants's sociodemographic data form, IRLSSG severity scale, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (EUI), and Beck Depression Inventory (BDI) were filled up by senior neurologists. Frequency of depressive symptoms, excessive daytime sleepiness, and poor sleep quality were examined.

Results: 122 patients (94 [77%] female and 28 [23%] male) diagnosed with primary RLS/WED according to IRLSSG criteria were included into the study. The severity level of RLS/WED in 19 (15.5%) of the patients was mild-moderate, 65 (53,2%) were severe, and 38 patients (31,2%) were very serious. BDI mean score of RLS/WED patients is 15.2±9 and EUI mean score of RLS/WED patients is 5±3.7. There was no statistically significant difference between the groups determined according to the severity of the disease. PSQI mean score of RLS/WED patients is 9.5±3.8. There was statistically significant difference between the groups determined according to the severity of the disease. Significant differences between the groups of RLS/WED patients were found on PSQI, especially in sleep duration, efficiency, and daytime sleep dysfunction.

Conclusion: Many diseases such as depression accompany with RLS/WED. Early recognition and treatment of these comorbid conditions is very important for the clinical progression of the disease.

Keywords: Depression; restless leg syndrome; sleep quality.

ÖZET

Amaç: Huzursuz bacak sendromu (HBS; diğer adıyla Willis-Ekbom hastalığı) iyi bilinen sensörimotor bir bozukluktur. Hasta bireylerde uyku fragmantasyonu sonucunda yaşam kalitesi etkilenmiş, anksiyete ve depresyon görülme sıklığı artmıştır. Bu çalışmanın amacı, HBS'nin uyku kalitesi, psikososyal yaşam üzerindeki etkileri ve hastalık şiddeti ile ilişkisini ortaya çıkarmaktır.

Yöntem: Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu tanı kriterlerine göre, toplam 122 hastaya HBS tanısı konuldu. Tüm katılımcıların sosyodemografik veri formu, Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu Şiddet Ölçeği, Pittsburgh Uyku Kalitesi İndeksi (PSQI), Epworth Uykululuk Ölçeği (EUI) ve Beck Depresyon Envanteri (BDI) nöroloji uzmanları tarafından dolduruldu. Depresif belirtilerin sıklığı, gündüz aşırı uykululuk hali ve kötü uyku kalitesi karşılaştırmalı olarak incelendi.

Bulgular: Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu kriterlerine göre, primer HBS tanısı almış 122 hasta (94'ü [%77] kadın, 28'i [%23] erkek) çalışmaya dahil edildi. Hastaların 19'unda (%15,5) HBS şiddet düzeyi hafif-orta, 65'inde (%53,2) şiddetli, 38'inde (%31,2) çok ciddi olarak tespit edildi. HBS hastalarının Beck Depresyon Envanteri ortalama puanı 15,2±9 ve HBS hastalarının Epworth Uykululuk Ölçeği ortalama puanı 5±3,7 olarak bulundu. Hastalığın şiddetine göre belirlenen gruplar arasında istatistiksel olarak anlamlı fark saptanmadı. HBS hastalarının Pittsburgh Uyku Kalitesi İndeksi puan ortalaması 9,5±3,8 olarak bulundu. Hastalığın şiddetine göre belirlenen gruplar arasında istatistiksel olarak anlamlı fark saptandı. Pittsburgh Uyku Kalitesi İndeksinde HBS hasta grupları arasında özellikle uyku süresi, verimliliği ve gündüz uyku bozukluklarında önemli farklılıklar tespit edildi.

Sonuç: HBS'ye depresyon gibi birçok hastalık eşlik eder. Bu komorbid durumların erken tanınması ve tedavisi hastalığın klinik seyri için çok önemlidir.

Anahtar sözcükler: Depresyon; huzursuz bacak sendromu; uyku kalitesi.

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Restless legs syndrome (RLS)/Willis-Ekbom disease (WED) is a well-known neurological sensory motor disorder which is characterized by an unpleasant sensations in the lower extremities and irresistible urge to move.[1] Symptoms usually begin in the evening or at night and it can be gradually intensify but resolve by the early hours of the morning. After a time of relative inactivity, the symptoms appear.[2] As the severity of RLS increases, these sensory complaints rarely cover other body parts such as hips, thighs, arms, or face "as shown in Figure 1".[3] Approximately, 50% of patients' complaints are observed in conditions where movement is restricted.[4]

The prevalence of RLS/WED is not clearly known due to methodological differences in epidemiological studies. The prevalence range varies between 0.1% and 15%. Women are affected twice as much as men and the incidence increases with the age.[5] There are two common epidemiological groups: early onset (age below 45 years) and late onset (age over 45 years). Early-onset RLS/WED is commonly familial and it is associated with autosomal dominant pattern of inheritance. Progression of early-onset form is slow. On the other hand, late-onset RLS/WED has rapidly progression and often associated with other comorbidities such as iron deficiency and renal failure. Although its incidence increases in older ages, it can also be seen in the pediatric population.[6]

According to etiology, RLS/WED is divided into two groups as primary and secondary. All secondary causes (neuropathy, diabetes, and pregnancy) should be ruled out to diagnose primary RLS/WED that constitutes 70–80% of all RLS/WED cases. There is no specific laboratory test for diagnosing RLS and it is based on the International RLS/WED Research Group's Standardized Clinical Diagnostic Criteria (IRLSSG).[7]

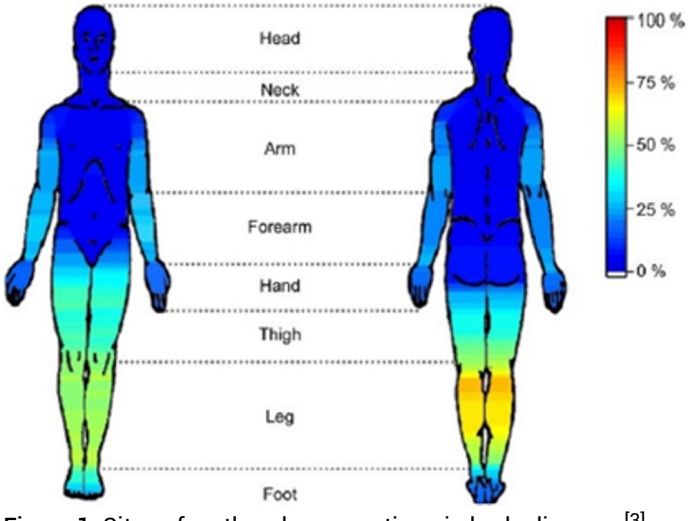

Figure 1. Sites of restless leg sensations in body diagram.[3]

It has been determined that the most important factor in RLS/WED pathophysiology is iron metabolism and dopaminergic system disregulation.[8] Recently, abnormal iron metabolism, multiple neurotransmitters, and central opiate system involvement have been defined. Some structural changes in various spinal cord and cortex areas have identified with neurophysiology studies. Furthermore, several genetic variants which are associated with risk of RLS/WED have been described by new genetic analysis techniques.[9]

RLS/WED can be treated by pharmacological and non-pharmacological therapies and the management needs long-term interventions. In clinical trials, various therapies have been tested. As a first-line therapy, dopamine agonists (such as pramipexole, ropinirole, and rotigotine) and calcium channel alpha-2-delta ligands are recognized. For the second line, benzodiazepines and opioids are seen as choices for treatment. Surely, clinicians should be aware of other causes and manage underlying disease with related departments.[10-12] In spite of initial remediation and positive response in majority of patients, problems such as loss of efficacy over time, side effects, and augmentation can be shown. The physician must be aware of the other therapeutic choices.[13,14]

Patients' sleep is severely affected as symptoms appear or worsen in the evening and at rest. As a result of sleep fragmentation, quality of life has affected.[15] In addition, incidence of anxiety and depression increases.[16] These are showing that treatment of the RLS/WED is possible not only with medical treatment but also by managing its psychosocial aspects. Our aim with this study is to obtain the effects of RLS/WED on sleep quality and psychiatric well-being and their relationship with disease severity.

Methods

In total, there are 122 RLS/WED patients who were followed in University of Health Sciences Haydarpaşa Numune Training and Research Hospital outpatient clinics of neurology. They were diagnosed with RLS/WED according to the International RLS Study Group (IRLSSG) diagnostic criteria.

All partipicants's sociodemographic data form, IRLSSG Severity Scale, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (EUI), and Beck Depression Inven-

tory (BDI) were filled up by senior neurologists. Patients were divided into subgroups according to the IRLSSG scale score as mild, moderate, severe, and very serious. The frequency of depressive symptoms, excessive daytime sleepiness, and poor sleep quality were determined according to the responses.

IRLSSG scale consists of 10 questions, each scored between 0–4 and asked about the typical symptoms of the disease to determine the severity of the disease. 0–10 points are evaluated as mild, 11–20 points as moderate, 21–30 points as serious, and 31–40 points as very serious RLS.[17]

BDI was created by Beck.[18] BDI's validity and reliability studies were conducted in our country by Hisli.[19] Scores can range from 0 to 63. The lowest score for any question is 0, and the highest score is 3. A score ≥17 indicates the risk for depression. PSQI is a type of sleep disorder scale that evaluates the quality of sleep over the past 1 month and provides data on the severity of sleep disorder.[20] Turkish validity and reliability study of the scale were made by Ağargün et al.[21] PSQI consists of 7 components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. If the total score ranging from 0 to 21 is above 5, it indicates "poor sleep quality".

EUI is a scale used to show daytime sleepiness. It consists of 8 questions, each with a score of 0–3. The possibility of falling asleep in ordinary day is questioned. If the total score is 10 and above, it indicates the presence of excessive daytime sleepiness.[22]

Ethical Approval

The study was approved by University of Health Sciences Haydarpaşa Numune Training and Research Hospital, Date: 04.11.2019, decision number: HNEAH-KAEK 2019/KK/149. This article was done in accordance with the Declaration of Helsinki with the approval of the ethics committee.

Statistical Analysis

Statistics were analyzed by IBM Statistical Package for the Social Sciences 21 package program. Normality distribution was decided by normality tests. Moreover, Chi-square test was used in the analysis of categorical variables. The Kruskal–Wallis test was used to compare the continuous variables of more than two independent groups. Pairwise comparison was performed using the Mann–Whitney U-test to determine which groups caused the difference between the variables found to be significant in the Kruskal–Wallis test. Below 0.05 of p-value was considered as statistically significant.

Results

122 patients (94 [77%] female and 28 [23%] male) diagnosed with primary RLS/WED according to the IRLSSG criteria were included into the study. The ages of the participants are between 18 and 65 and the average age is 47.8.

The severity level of RLS/WED in 19 (15.5%) of the patients was mild-moderate, 65 (53.2%) were severe, and 38 patients (31.2%) were very serious. The number of patients with mild disease level was insufficient for statistical evaluation because of that mild and moderate patient groups were evaluated together.

BDI mean score of RLS/WED patients is 15.2±9. There was no statistically significant difference between the groups determined according to the severity of the disease. According to the BDI, 69%, 7 (n=85) of the patients had depressive symptoms and major depression was found in 5 patients (4.1%). On the other hand, depressive symptoms severity was significantly higher in very severe group than mild-moderate group ($p<0.05$).

EUI mean score of RLS/WED patients is 5±3.7. There was no significant difference between the groups determined according to the severity of the disease. According to the EUI, 11.4% (n=14) of the patients had excessive daytime sleepiness.

PSQI mean score of RLS/WED patients is 9.5±3.8. The distribution of PSQI scores is shown in Table 1. There was statistically significant difference between the groups determined according to the severity of the disease. The group with mild-moderate received statistically significantly lower scores from the very severe group ($p=0.02$) and the severe group lower scores from the very severe group ($p=0.001$).

Significant differences between the groups of RLS/WED patients were found on PSQI. Mild-moderate group sleep quality was frequently better than the very severe group ($p=0.03$). Sleep duration was found to be shorter in very severe group than the severe group ($p=0.006$). There was a significant difference between very severe group and the severe group for the sleep efficiency ($p=0.017$). Finally, daytime sleep dysfunction was prominent in very severe group compare to mild-moderate ($p=0.008$) and severe groups ($p=0.014$).

Table 1. Distribution of Pittsburgh sleep quality index scores

n:122	Mild	Severe	Very severe	Total	p*
Pittsburgh Sleep Quality Index					
Global score	8.1±3.1	8.9±3.8	11.3±3.6	9.5±3.8	0.001
Sleep quality	0.8±1	1.1±0.9	1.6±0.8	1.25±1	0.008
Sleep latency	1.6±0.7	1.9±0.7	1.9±0.8	1.9±0.8	0.17
Sleep duration	1.2±1.1	1.1±1.1	1.7±1.1	1.34±1.16	0.01[b]
Sleep efficiency	1.1±1	1±1.2	1.5±1.2	1.2±1.2	0.04[b]
Sleep disturbance	1.4±0.6	1.7±0.6	1.8±0.6	1.75±0.63	0.07
Sleep medication	0.5±0.8	0.4±0.9	0.8±1.2	0.58±1	0.26
Daytime sleep dysfunction	0.8±1	1.1±0.9	1.6±0.9	1.25±1	0.008

*[a]Significant difference between mild/moderate and very severe groups. [b]Significant difference between severe and very severe groups. [c]Significant difference between mild/moderate and severe groups.

The clinical and demographic characteristics of the groups according to the disease severity are summarized in Table 2.

Discussion

RLS/WED is a common neurological disorder that increases in frequency with age. The most common impairment seen in RLS/WED patients is insomnia, which has a direct effect on well-being and daily functioning.[15] Although insomnia is the most common presenting complaint, pain, stress and fatigue are also associated with inadequate sleep.

Sleep impairment can cause depressive disorders. Consequently, RLS/WED patients have remarkable scores of depression and anxiety.[23] Furthermore, in our study, depressive symptoms were detected in 69.7% (n=85) of the patients. As it was shown with epidemiologic studies, the prevalence of psychiatric disorders was higher in patients with RLS than in patients without RLS symptoms.[24] Similarly, we showed that depression frequency was high (57,9%) in mild-moderate group. It was approximately 72% in other groups. RLS-related insomnia can conceivably lead to depression. Insomniacs are believed to have a higher risk of acquiring new depression than individuals who do not experience insomnia. As a result, there are various probable explanations for RLS patients' past diagnosis of depression. Furthermore, the comorbidity of RLS with depression may be due to the role of dopaminergic pathophysiological mechanisms.

There is a strong relationship between insomnia and depression. RLS symptoms usually occur at night. It is difficult for RLS/WED patients fall asleep. Especially, sleep duration, sleep quality, and daytime activity are affected. Hence, depressive symptoms can occur or get worsen.[25]

We showed that with PSQI, 72% of RLS/WED patients (n=88) had daytime dysfunction. 14 patients got a score of 10 and more on the EUI so 11.4% of the patients had excessive day-

Table 2. Clinical and demographic characteristics of patients

	Mild/Moderate (n=19)	Severe (n=65)	Very severe (n= 38)	Total (n=122)	p
Age (Med±SD) (Median)	54.1±8.2 (56)	46.4±12.4 (48)	47±13.4 (49.5)	47.8±12.4	0.07**
Gender F/M, n (%)	12 (63.2%)	50 (76.9%)	32 (84.2%)	94 (77%)	0.2*
	7 (36.8%)	15 (23.1%)	6 (15.8%)	28 (23%)	
EUI (Med±SD) (Median)	4.9±3 (5)	4.6±3.2 (4)	6±4.7 (5.5)	5±3.7	0.65**
BDI (Med±SD) (Median)	12.1±7.5 (10)	14.7±8.2 (14)	17.7±10.3(17.5)	15.2±9	0.11**
Depression -/+, n (%)	8 (42.1%)	18 (27.7%)	11 (28.9%)	37 (30.3%)	0.47*
	11 (57.9%)	47 (72.3%)	27 (71.1%)	85 (69.7%)	
PSQI (Med±SD) (Median)	8.1±3.1 (8)	8.9±3.8 (9)	11.3±3.6 (11.5)	9.5±3.8	0.001**[a,b]

*χ^2 test. **Mann–Whitney U, Kruskal–Wallis. [a]Significant difference between mild-moderate and very severe groups (p=0.02). [b]Significant difference between severe and very severe groups (p=0.001). EUI: Epworth Sleepiness Scale; BDI: Beck Depression Scale; PSQI: Pittsburgh Sleep Quality Index; Med: Median; SD: Standard deviation.

time sleepiness. As the severity of the disease increases, the negative impact on sleep quality becomes more prominent. As a result, there may be loss of workforce and cause both social and economic problems.

According to BDI, 28.6% of RLS/WED patients (n=35) had moderate to severe depression and symptoms became more serious by the severity. It could be the result of sleep problems seen in RLS/WED patients and daytime dysfunction. As the severity of the disease increases, deterioration in sleep quality and depressive symptoms also support this view. On the other hand, RLS/WED and mood disorders (especially depression) may have similar neurobiological pathways. It can be explained by the comorbidity of common neurobiological origin with mood disorders and RLS/WED.

Dysregulation of dopaminergic metabolism can be a potential denominator of both RLS/WED and mood disorders. Down regulation of the dopamine receptor coupled with low nightly dopamine activity can trigger a state of dopamine deficiency at night, so symptoms of RLS/WED occur. Dopaminergic medications are highly effective in RLS/WED. This can be corrected for a relative night decrease in dopamine.[26] Furthermore, RLS/WED effects are exacerbated by dopamine receptor antagonists such as metoclopramide and antipsychotic medications. In addition, dopamine receptor sensitivity reduction and decreased of dopamine turnover play a main role in depression.[27]

There are some difficulties in the diagnosis and treatment of depressive disorder in RLS/WED patients. RLS/WED symptoms can cause some depression symptoms such as insomnia, loss of energy, demotivation, and psychomotor retardation. In many cases, it can be difficult to determine whether these symptoms are the result of depression or related to RLS.

On the other hand, antidepressant drugs such as escitalopram, fluoxetine, sertraline, and mirtazapine can affect RLS/WED. Clinicians should be aware of medications that may exacerbate the symptoms of RLS/WED.[28] In general, drug-induced RLS/WED resolves with dose reduction or withdrawal.

The development of comorbid depression in patients with RLS/WED can be avoided by education about depressive behavioral patterns. In particular, patients benefited from activities focused on mindfulness and stress control techniques.[29]

Conclusion

RLS/WED causes pathological fatigue but responds to appropriate treatment. Although RLS/WED is a benign disease, delays in diagnosis may have socioeconomic consequences. Early recognition and treatment of these comorbid conditions are very important for the clinical progression of the disease.

Disclosures

Ethics Committee Approval: The study was approved by University of Health Sciences Haydarpaşa Numune Training and Research Hospital, Date: 04.11.2019, decision number: HNEAH-KAEK 2019/KK/149.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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