Original Article / Çalışma - Araştırma

The Comorbidities Accompanied by Restless Leg Syndrome: Anxiety and Depressive Disorders Rank First

Huzursuz Bacak Sendromuna Eşlik Eden Komorbiditeler: Anksiyete ve Depresif Bozukluklar İlk Sırada

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Objectives: In this study we analyzed the effect of diseases such as anemia, renal failure, rheumatoid arthritis, fibromyalgia and peripheral neuropathy to the restless leg syndrome (RLS).

Patients and Methods: Four thousand five hundred patients, who have been seen in the general neurology clinic between January 2007 and December 2009 were evaluated retrospectively and 76 RLS cases were selected. Re-evaluation has been proposed to the patients with telephone calls. Fifty-five patients (36 females, mean age 55±14 years; 19 males, mean age 61±11 years) accepted the invitation and were re-evaluated. Neurological examinations and biochemical analysis has been made. Beck Depression and Anxiety scales were also applied to all patients.

Results: Seventy-six patients (1.2%) admitted to the general neurology clinic had been diagnosed with RLS. Mild-moderate depression was noted in 29 patients (52.7%) and generalized anxiety disorder was found in 26 patients (47.3%). Other comorbid diseases were iron deficiency anemia (14.5%), type 2 diabetes mellitus (14.5%), idiopathic Parkinson disease (3.6%), lumbar disc herniation (27.3%), hypertension (49.1%), coronary artery disease (32.7%) and obstructive sleep apnea syndrome (16.4%).

Conclusion: Many physical and mental disorders can be associated with RLS. Our results mostly support that, there is a clear association with anxiety, depressive disorders and RLS. This association might be due to reciprocal interactions and common pathophysiologies. Further examinations including experimental models are needed.

Key Words: Anxiety disorders; comorbid disorders; depressive disorders; parkinsonism; restless leg syndrome.

Amaç: Bu çalışmada anemi, böbrek yetmezliği, romatoid artrit, fibromiyalji ve periferik nöropatiler gibi hastalıkların huzursuz bacak sendromu (HBS)'na etkisi araştırıldı.

Hastalar ve Yöntemler: Ocak 2007 - Aralık 2009 tarihleri arasında genel nöroloji polikliniğimizce takipleri yapılan 4500 hasta geriye yönelik olarak incelendi ve 76 HBS olgusu seçildi. Yapılan telefon görüşmeleriyle hastalara yeniden değerlendirilme önerildi. Elli beş hasta (36 kadın, ort. yaş 55±14 yıl; 19 erkek, ort. yaş 61±11 yıl) daveti kabul etti ve yeniden değerlendirildi. Nörolojik muayeneleri ve biyokimyasal incelemeleri yapıldı. Ayrıca tüm olgulara Beck Depresyon ve Anksiyete ölçekleri de uygulandı.

Bulgular: Genel nöroloji polikliniğine başvuran 76 hastaya (%1.2) HBS tanısı konuldu. Hafif ve orta düzeyde depresyon 29 olguda (%52.7), anksiyete bozukluğu 26 olguda (%47.3) saptandı. Eşlik eden diğer hastalıklar ise demir eksikliği anemisi (%14.5), tip 2 diyabetes mellitus (%14.5), idiyopatik Parkinson hastalığı (%3.6), lomber disk hernisi (%27.3), hipertansiyon (%49.1), koroner arter hastalığı (%32.7) ve tıkayıcı uyku apne sendromu (%16.4) olarak saptandı.

Sonuç: Birçok ruhsal ve fiziksel bozukluklar HBS ile birlikte görülebilmektedir. Sonuçlarımız anksiyete, depresif bozukluklar ile HBS arasında net bir ilişki varlığını yüksek oranda desteklemektedir. Bu durum, iki hastalık arasındaki karşılıklı etkileşime ve ortak patofizyolojilere bağlı olabilir. Deneysel modelleri de içeren ileri çalışmalar gereklidir.

Anahtar Sözcükler: Anksiyete bozukluğu; komorbid bozukluklar; depresif bozukluk; parkinsonizm; huzursuz bacak sendromu.

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Received / *Geliş tarihi:* December 15, 2010 Accepted / *Kabul tarihi:* January 29, 2011

Restless leg syndrome (RLS) is a disorder in which people experience a strong urge to move their legs or other extremities during rest.[1] The urge to move is usually accompanied by an unpleasant and uncomfortable sensation in the affected limb that may be described as creeping, crawling, tingling, pulling, or painful, and it commonly affects sleep. Typically the legs are mostly affected but arm involvement has also been reported. The sensations are temporarily relieved by movement and have a strong circadian pattern, with symptoms worsening in the evening and at night and often diminishing in the morning after sleep.[2-4]

Restless leg syndrome affects many people. General population prevalence surveys usually range from 1% to 12% but most European ancestry studies suggest 10%.[5]

Studies of the prevalence of RLS suggest that a significant proportion of the elderly population has symptoms of the disorder and that the prevalence is somewhat greater in women than in men.[4,6] In fact, careful history reveals that 38-45% of adults suffer from RLS. The initial onset of symptoms occurs before 20 years of age.[7] In one study the prevalence of RLS was found to be 3.4% of the Turkish population aged over 18, however it was seen that RLS increases with age in both genders in this population.[8] It appears that RLS is also common in children with an estimated prevalence of 1.9% in school-aged children.[9,10]

It is commonly believed that RLS has a genetic component. Clinical surveys have shown that in idiopathic forms of the disease, 40.9-92% of patients report having a family history of RLS. Although clinical features do not differ between familial and sporadic cases of RLS, familial RLS significantly correlates with an earlier age of onset and a slowly progressive development of symptoms.[7,11,12]

The objective of our study was to assess the prevalence, demographic factors and comorbidities of idiopathic and symptomatic RLS in an outpatient neurology clinic.

PATIENTS AND METHODS

The card information of the 76 RLS patients seen in the neurology clinic between 2007 and 2009 were accessed. A telephone interview was made with them, and they were invited to our clinic. Fifty-five RLS patients (36 female; mean age 55±14 years; and 19 males, mean age 61±11 years) accepted the invitation and they were re-evaluated.

Diagnosis of RLS was made by a specialist on the basis of the four standard criteria defined by the International RLS study group: *(i)* an urge to move (mainly the legs), usually accompanied or caused by uncomfortable and unpleasant sensations in the limbs; *(ii)* these symptoms begin or worsen during periods of rest or inactivity; *(iii)* symptoms are partially or totally relieved by movement (at least as long as the activity continues); and *(iv)* symptoms are worse or only occur in the evening or night.[13] The patients met the diagnostic criteria of The International Restless Legs Syndrome Study Group (IRLSSG).

The age-at-onset of RLS, demographic data and presence or absence of RLS in first-degree relatives was determined in all patients. The presence of associated conditions (secondary RLS) was determined by clinical interviews, and complete physical and neurological examinations and blood chemistries were done. Beck depression and anxiety scales were also applied to all patients.

Restless leg syndrome subjects were subsequently asked about severity using the International Restless Legs Syndrome Study Group (IRLSSG) rating scale.[14] This subjective scale consists of 10 questions about RLS symptoms, including five items pertaining to symptom frequency and intensity and five items addressing the impact of symptoms on aspects of daily living and sleep with a maximum disability score of 40. We used a validated Turkish version of the severity scale. According to the symptom frequency and intensity, the subjects were grouped into four categories: mild, moderate, severe, and very severe (1-10 points= mild, 11-20= moderate, 21-30= severe, 31-40= very severe).[15]

Our local ethics committee approved the study. Before enrollment, patients received detailed written and verbal information regarding

the aims and protocol of the study and signed informed consent.

Statistical analysis

The data analyses were performed with the SPSS version 16.0 software (SPSS, Inc. Chicago, IL, USA). Variables were analyzed using descriptive statistics, Mann-Whitney U-test and Pearson's correlation analysis. A p-value of <0.05 was considered significant.

RESULTS

The mean of IRLSSG rating scale score was 26.4±5 (range 20-40). According to symptom frequency and intensity, RLS was moderate in 5.5% (scoring between 11 and 20), severe in 74.5% (scoring between 21 and 30) and very severe in 20% (scoring between 31 and 40) of the patients. A family history of RLS was reported in 28% and 18.2% of the patients arms were also affected.

Thirty-six (65%) patients received a diagnosis of primary RLS and 19 (35%) received a diagnosis of secondary RLS. Mild-moderate depression was noted in 29 patients (53%). The mean Beck Depression Score was 22±4 (range 15-30). Among the patients with depression, 17% were mild, 74% were moderate and 9% were severe. Anxiety disorder was found in 26 patients (47%) with RLS. The mean Beck Anxiety Score was 26±5 (range 13-40). Among the patients with anxiety, 4% were mild, 40% were moderate and 56% were severe. A significantly high proportion of depression was found in RLS patients with anxiety (92.3% and 17.2% respectively, p<0.0001). When the RLS patients with anxiety and those without anxiety were compared, a significant difference in hypertension was noted (65.4% and 34.5% respectively, p=0.02). With correlation analysis, a significant negative correlation was found between age and Beck Anxiety Score (r=–0.52, p=0.007). A significant positive correlation was found between the RLS severity scale and Beck Anxiety Scale (r=0.41, p=0.03). A significant positive correlation was found between the periodic limb movements during sleep (PLMS) index and Beck Anxiety Score (r=0.99, p=0.02).

Ten patients underwent one night of polysomnographic recording in the sleep laboratory with a diagnosis of obstructive sleep apnea syndrome (OSAS). Sleep was recorded and scored according to the standard method.[16] Electromyograms from both anterior tibialis muscles were recorded to score periodic limb movement (PLM) and scoring was made according to Coleman's criteria.[17] The periodic limb movements during sleep index were found to be 29.8±19 (range 6 to 76). The prevalence of comorbidities of RLS patients in our study is shown in table 1.

DISCUSSION

Restless legs syndrome prevalence surveys usually range from 1 to 12%. In a study conducted in a Turkish population, the prevalence of RLS was found to be 3.4% in the Northern part of Turkey, and 3.19% in the Mediterranean coast of Turkey.[5,8,15,18-20] It may start at any age, but there is a demonstrated increase in RLS among the elderly with a female preponderance.[6] In our study, we found that RLS prevalence increases with age and most severely affected patients were women like the previous studies. The movements usually involve the legs, but in severely affected RLS patients, the arms may also be involved.[12] In our study group 18.2% of our patient's arms were affected.

The etiology of RLS is poorly understood. Among the elderly population, RLS is associated with other diseases such as iron deficiency, renal failure, diabetes mellitus, peripheral

Table 1. Prevalence of comorbidities in restless leg syndrome patients

	%
Depression	52.7
Hypertension	49.1
Anxiety disorder	47.3
Coronary disease	32.7
Lumbar disc herniation	27.3
Hyperlipidemia	25.5
Obstructive sleep apnea syndrome	16.4
Diabetes mellitus	14.5
Iron deficiency anemia	14.5
Smoking	12.7
Chronic obstructive pulmonary disease	7.3
Alcohol consumption	3.6
Parkinsonism	3.6

neuropathy and various other conditions such as rheumatoid arthritis, lumbosacral radiculopathy and fibromyalgia.[5] Several neurodegenerative disorders such as Parkinson disease (PD) and multiple system atrophy that usually occur among elderly patients can also be the cause of RLS. Restless leg syndrome can also be associated with smoking, respiratory symptoms and decreased lung function. These are considered secondary forms of RLS. In absence of those medical disorders, RLS is called ''primary'' or ''idiopathic'' RLS.[5,21] The most frequent form of this condition is the idiopathic form and 65% of the patients in our study were in this form. Several conditions have been shown to be associated with RLS, but in none of these conditions is the exact relationship with RLS understood.[21]

In our study, hypertension was found in 49.1% of RLS patients. Previous studies have looked at the risk of cardiovascular disease in RLS populations.[22] Ulfberg et al.[18] found that the RLS group had a significant odds ratio (OR) of 2.5 for ''heart problems'' and a non-significant OR of 1.5 for hypertension compared to those without RLS. In the polysomnographic (PSG)studies conducted on RLS patients, they found that periodic leg movements throughout the night were associated with an increase in blood pressure. Periodic leg movements can affect hypertension or other cardiovascular factors.[13,22,23] Our study did not find a statistically significant difference between the mean PLMS index and hypertension.

The frequency of anemia in our study was 14.5%. Iron metabolism has been extensively evaluated in RLS. There is a frequent association between RLS, anemia and low serum levels of ferritin. Several studies have shown that RLS severity correlates with serum ferritin levels, even for ferritin in the normal range, suggesting the possibility of treating RLS with iron supplementation.[2,24]

The main finding of our study was that RLS patients are at increased risk for anxiety and depressive disorders. Gorman and Dyck[25] first found higher scores on depression and psychasthenia scales in RLS patients. Sevim et al.[15] confirmed that the RLS population was more anxious and depressed than controls. Rothdach et al.[6] also found higher depression scores in men. In our study mild-moderate depression was found in 52.7%, and anxiety disorder was found in 47.3%. No difference was found with respect to gender in the patients with anxiety and depression.

Possible mechanisms by which RLS increases the risk of specific depressive and anxiety disorders are not known at the moment. It is well known that sleep disturbances can increase the risk of depressive disorders.[26,27] Restless leg syndrome interferes with sleep and induces insomnia.[2,7,28,29] Insomnia in turn is a risk factor for depression and insomnia itself can increase the activity of hormones and pathways in the brain that produce emotional problems.[30] Previous authors have reported a correlation between the degree of sleep impairment and the severity of mood disturbance.[29,31]

May RLS cause anxiety and depression or may psychiatric symptoms cause RLS? This relation is still not well known. Sevim et al.[15] could not claim definitely from their data that higher anxiety and depression are the consequences of RLS. Neither could we say that anxiety disorder symptoms might be caused by the RLS symptoms. The temporal relationship between anxiety, depression and RLS suggests that RLS is as the primary condition in most cases. Winkelmann et al.[11] mentioned these mental disorder symptoms might be caused by their RLS symptoms.

Restless leg syndrome is a highly familial disorder. The increased risk of specific depressive and anxiety disorders could have a genetic etiology as well, and whether both the neurological and psychiatric conditions segregate within the same families needs to be investigated.[11,32] The presence of a family history of RLS was 28.3% in our study group but we have no data available on the relationship between familial RLS and anxiety/depression symptoms in our patient group.

The severity of RLS symptoms is important for the physician in deciding the patient's need for pharmacotherapy and selection

of the accurate drug. But in the presence of anxiety and depression, the effects of levodopa, dopaminergics and antidepressants on anxious and depressive symptoms among RLS patients must be investigated in order to determine the best treatment strategy.[15] The medication used for the treatment of RLS such as dopaminergic, gamma aminobutyric acid A (GABAA)-ergic and opioidergic compounds may also influence the development of depression and anxiety disorders in RLS patients. Although many review articles mention an association between antidepressant use and restless legs, Winkelmann et al.[32] could not detect any differences between RLS patients treated and untreated with antidepressants. Moreover, there were no statistical associations between RLS and antidepressant use in a study of Brown et al.[33] In our study, the patients had been treated with GABAA-ergic, seratonergic dopamin agonists. We could not find that the RLS symptoms were increased with these drugs. Long-term studies with different drugs are needed.

In conclusion, our study points out as the first major issue the importance of hypertension in secondary RLS. Secondly, it points out the close association of RLS with anxiety disorders and depression, and the close correlation of RLS severity grade to anxiety and depression scores. Between these psychiatric disorders and RLS exists a connection, the causality of which cannot be clearly identified. Longer-term studies including more cases, which also evaluate the effects of anxiety and depression treatment on RLS are needed.

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