

# Restless Legs Syndrome and Migraine

## Huzursuz Bacak Sendromu ve Migren

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**ABSTRACT Objective:** Based on the literature about the association between restless legs syndrome (RLS) and migraine, we designed our study to investigate the relationship of these two conditions among students of Ordu University via questionnaire. **Material and Methods:** We enrolled 198 participants (82 female, 116 male) aged 19.97±2.07 years. Firstly, the participants were evaluated as migraine (+) and migraine (-) and then, all participants were divided into four groups; group 1: migraine with RLS (n=20), group 2:only migraine (n=19), group 3:only RLS (n=19), group 4: without migraine and RLS (n=140). Participants were firstly asked about personal information, sleep, habits (smoking, alcohol, caffeine) and medical history. Participants were asked the four essential diagnostic criteria of International Restless Legs Study Group (IRLSSG). If RLS was diagnosed, severity was diagnosed using IRLSSG rating scale. Diagnosis of migraine was made according to International headache Society criteria for migraine. To measure the disability related with headache, Migraine Disability Assessment questionnaire was used. **Results:** The results of our study demonstrated that the migraine was significantly associated with RLS and participants with migraine tend to have worse RLS scores and severity. Between four group females were significantly higher in grup 1 than grup 4. Sleep disturbances were significantly frequent in group 1 and 3 than grup 4, caffeine intake were significantly frequent in group 1 than grup 4. The prevalence and severity of RLS, frequency of sleep problems and caffeine intake, female/male ratio were significantly higher in grup with migraine. None of the participants who were accepted as migraine and/or RLS admitted a physician for their symptoms. **Conclusion:** Our study demonstrates an association between RLS and migraine, and it also reflects that sleep disturbances and caffeine intake contribute this association.

**Key Words:** Restless legs syndrome; migraine disorders; comorbidity

**ÖZET Amaç:** Huzursuz bacak sendromu (HBS) ve migren arasındaki ilişkiyi literatür ışığında araştırmayı amaçlayarak, Ordu Üniversitesi öğrencileri arasında anket yoluyla bu iki hastalığın birlikteliğini sorguladık. **Gereç ve Yöntemler:** Çalışmaya yaş ortalaması 19,97±2,07 yıl olan 198 katılımcı (82 kız, 116 erkek) dahil edildi. Katılımcılar öncelikle migren (+) ve migren (-) olarak ayrıldı. Daha sonra tüm katılımcılar; grup 1:HBS ve migren (n=20), grup 2:sadece migren (n=19), grup 3:sadece HBS (n=19), grup 4: migren ve HBS olmayan (n=140) olmak üzere dört gruba ayrıldı. Katılımcılara öncelikle kişisel bilgiler, uyku alışkanlıkları (sigara, alkol, kafein) ve tıbbi özgeçmişleri hakkında sorular soruldu. Katılımcılara Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu nun (UHBSÇG) dört temel tanı kriteri soruldu. HBS tanısı varsa, şiddeti UHBS-ÇG şiddet ölçeği kullanılarak belirlendi. Migren tanısı Uluslararası başağrısı derneği tarafından belirlenen migren tanı kriterlerine göre yapıldı. Başağrısıyla ilişkili yaşamdan alınmayan değerlendirmek için migren yeti yitimi değerlendirme ölçeği kullanıldı. **Bulgular:** Çalışmamızın sonuçları migren ile HBS arasında anlamlı bir ilişki olduğunu ve migrenli olan katılımcıların HBS puanları ve şiddetinin daha kötü olma eğiliminde olduğunu göstermiştir. Dört grup arasında kız öğrencilerin grup 1'de grup 4'e göre anlamlı olarak daha yüksek olduğu gözlemlendi. Uyku bozuklukları grup 1 ve 3'te grup 4'e göre anlamlı olarak daha sık bulundu. Kafein alımı grup 1'de grup 4'e göre anlamlı olarak daha sıkı. HBS sıklığı ve şiddeti, uyku sorunları ve kafein alımı sıklığı, kadın/erkek oranı migrenli grupta anlamlı olarak yüksek bulundu. Migren ve/veya HBS olarak kabul edilen katılımcılar hastalıklarıyla ilişkili daha önce hekime başvurmamışlardı. **Sonuç:** Çalışmamız HBS ve migren arasında bir ilişki olduğunu, uyku bozuklukları ve kafein alımının bu birliktelikte katkısı olduğunu düşündürmektedir.

**Anahtar Kelimeler:** Huzursuz bacak sendromu; migren hastalıkları; eşzamanlı hastalık

**R**estless legs syndrome (RLS) is a condition characterized by uncomfortable sensations in legs and urge to move legs, with increase of symptoms in rest or inactivity and at night, relief of the symptoms by voluntary movements. RLS predominantly affects the women.<sup>1,2</sup> The prevalence of RLS varies from 2% to 15%.<sup>3</sup> Dysfunction of dopaminergic neurotransmitter system seems to be related to RLS. It is also proposed that peripheral mechanism like C-fibre neuropathy and spinal lesions may play a role.<sup>4</sup> It is mostly seen as idiopathic form and approximately 50% of the patients have a family history.<sup>5</sup> Secondary RLS is associated with some diseases such as anemia, pregnancy, renal failure, diabetes mellitus, hypothyroidism, polyneuropathy, arthritis, Parkinson disease (PD) and other sleep disorders.<sup>6-8</sup>

Migraine is characterized by headache attacks and predominantly affects the women. It is seen in 10%-20% of the population.<sup>9</sup> It is related to neurotransmitters like serotonin and calcitonin- gene related peptides.<sup>10</sup> Some studies reported the involvement of dopamine in pathophysiology of migraine.<sup>11,12</sup> Several diseases are described the comorbidity with migraine such as cardiovascular disease, stroke, depression, epilepsy, fibromyalgia and other pain disorders.<sup>13,14</sup> Migraine is related with insufficient sleep quality, decreased arousal index, somnambulism, prolonged sleep latency.<sup>15,16</sup>

RLS is reported in 17-34% of patients with migraine.<sup>17-19</sup> The exact mechanism remains unclear. It was suggested that different behaviour of dopamine, and maybe melatonin, in primary headaches reflect the risk for headache patients to have RLS.<sup>20</sup> It is considered that dopaminergic dysfunction of the A11 nucleus in hypothalamus explains the association of RLS and migraine.<sup>21</sup>

In this study, we aimed to investigate the association between migraine and RLS by using questionnaire among university students.

## MATERIAL AND METHODS

This study was conducted with the students of Ordu University. Participants were interviewed based on a questionnaire. We enrolled 198 participants (82

female, 116 male) aged 19.97±2.07. Participants were firstly asked about personal information, sleep, habits (smoking, alcohol, caffeine) and medical history. Participants were asked the four essential diagnostic criteria of International Restless Legs Study Group (IRLSSG).<sup>2</sup> Participants who answered 'yes' to all four questions were considered as RLS. If RLS was diagnosed, severity was diagnosed using IRLSSG rating scale (IRLS).<sup>22</sup> Total score ranges from 0 to 40. According to total scores severity stage was made as; 1-10 points: slight symptoms (1), 11-20 points: moderate symptoms (2), 21-30 points: strong (3) and 31-40 points: very strong (4). Diagnosis of migraine was made according to International headache Society (IHS) criteria for migraine.<sup>23</sup> To measure the disability related with headache, Migraine Disability Assessment (MIDAS) questionnaire was used,<sup>24</sup> and severity was made as; 1: 0-5 points, 2: 6-10 points, 3: 11-20 points, 4: 21 and over. To investigate the sleep disorders we did not use a specific scale. The participants were asked whether they have the following problems; 1) staying up, 2) difficulties to falling asleep, 3) frequent awakening, 4) difficulties to awake, 5) daytime sleepiness.

This study was approved by local ethics committee of Ordu University. Participants signed informed consent before entering the study.

We compared the characteristics of participants with and without migraine using t-test for continuous variables and chi-square test for categorical variables. In comparison between four groups; for categorical data chi-square test, for continuous variables one-way analysis of variance were used, when appropriate Bonferroni test was used for post-hoc analysis.

## RESULTS

Of all participants in 19.7% (n=39) migraine, in 19.7% (n=39) RLS were observed. Firstly, the participants were evaluated as migraine (+) and migraine (-) (Table 1) and then, all participants were divided into four groups; group 1: migraine with RLS (n=20), group 2: only migraine (n=19), group 3: only RLS (n=19), group 4: without migraine and RLS (n=140) (Table 2) to compare demographic and

**TABLE 1:** Demographic and clinical features of participants with migraine and without migraine.

	Migraine (+) (n= 39)	Migraine (-) (n= 159)	P value
Age (year)	20,30±2,06	19,90±2,07	0,27
Gender (female/male)	26/13	56/103	<0,001
Smokers (%)	23,1	21,4	0,82
Smoking (package year)	3,80±2,34	4,38±2,91	0,56
Alcohol (%)	2,6	6,3	0,36
Caffeine (%)	30,8	10,1	<0,001
RLS	51,3	11,9	<0,001
RLS score	19,20±6,22	13,79±4,39	<0,05
RLS severity (n)			
1	2	5	<0,001
2	8	13	
3	10	1	
Sleep disturbance (%)	61,5	31,4	<0,001

RLS. Restless legs syndrome.

**TABLE 2:** Demographic and clinical features of participants.

	Group 1 (n=20)	Group 2 (n=19)	Group 3 (n=19)	Group 4 (n=140)	P value
Age (years)	20.60±1.93	20±2.11	19.68±1.94	19.92±2.09	0.52
Gender (%) female	75	57.9	47.4	33.6	<0.05 <sup>a</sup>
MIDAS (n)					0.13
1	2	6	-	-	
2	11	7	-	-	
3	5	5	-	-	
4	2	0	-	-	
Sleep disturbance (%)	65	57.9	63.2	27.1	<0.001 <sup>a,b</sup>
Smokers (%)	25	21.1	10.5	22.9	0.30
Smoking (package year)	4.60±2.30	3.0±2.34	3.50±2.12	4.44±2.96	0.72
Alcohol (%)	-	5.3	-	7.1	0.17
Caffeine (%)	40	21.1	7	6.8	<0.001 <sup>a</sup>

<sup>a</sup> significant for group 1 vs group 4

<sup>b</sup> significant for group 3 vs group 4

clinical data. The prevalence and severity of RLS, frequency of sleep problems and caffeine intake, female/male ratio were significantly higher in group with migraine. Demographic and clinical features of participants were presented in Table 1 and 2. Between four groups females were significantly higher in group 1 than group 4. Sleep disturbances were significantly frequent in group 1 and 3 than

group 4, caffeine intake were significantly frequent in group 1 than group 4. All alcohol users in participants have spelled an intake of 1-2 per a year. None of our participants were aware of their migraine and/or RLS.

## DISCUSSION

Some neurological diseases appear frequently in migraine patients such as mood disorders, sleep disturbances, epilepsy, stroke and movement disorders.<sup>14</sup> The movement disorders-PD, essential tremor, dystonia- with involvement of dopaminergic system have been adhered to migraine.<sup>25-27</sup> RLS is also supposed to be a disease occurring as a result of dysfunction of dopaminergic system in the hypothalamic A11 nucleus.<sup>28,29</sup> The A11 nucleus inhibits firing in the trigeminocervical complex (TCC), sends inhibitory projections to preganglionic sympathetic neurons, dorsal and ventral horn. TCC is important for migraine information transmission from the head and orofacial structures to the hypothalamus.<sup>30</sup> Hence, the dysfunction of the A11 nucleus enables firing in the TCC, increases sympathetic activity, and may be causes migraine and RLS. In migraine, reduced release of serotonin could decrease the dopamine release and raises the extrastriatal receptor hypersensitivity. So, the dopaminergic system can explain the relationship between RLS and migraine. Furthermore, dopaminergic agents are used as standart therapy of RLS,<sup>31</sup> and antiemetics with antidopaminergic effects are used in the treatment of migraine attacks.<sup>32</sup> In an autopsy study, RLS patients showed increased tyrosine hydroxylase in substantia nigra that suggest iron insufficiency results in alteration in dopaminergic system.<sup>33</sup> Iron is a cofactor in dopamine synthesis and iron metabolism has been implicated in RLS development.<sup>8,34</sup> It is reported that iron levels may decrease in cerebrospinal fluid but not in serum.<sup>35</sup> Suzuki et al's results did not demonstrate difference between migraine patients with or without RLS for markers of iron metabolism.<sup>36</sup> Iron metabolism has also suggested to be associated with repeated attacks of migraine.<sup>37</sup> Brain iron storage has found in periaqueductal gray matter in migraineurs indicating the abnormal iron metabolism.<sup>38</sup>

The results of our study demonstrated that the migraine was significantly associated with RLS and participants with migraine tend to have worse RLS scores and severity. Our study showed a much higher prevalence of RLS in migraine than previous studies. It is probably due to the differences our study design, because we did not exclude the secondary causes of RLS. RLS diagnosis was based on the reply the questions of minimal criteria of IRLSSG,<sup>39</sup> but it does not have the power for differentiate the diseases, such as neuropathy, muscle cramps, arthritis, etc., which mimic RLS. Although, our target audience consist of young adult people and they did not report other medical history by self-report. We also did not apply any laboratory tests for differential diagnosis.

In our study, the participants with migraine and/or RLS have more frequent sleep problems than participants without both. By reason of our study based on a basic questionnaire form we did not verify the relevance of these sleep problems with objective methods. Sleep disturbances are commonly seen in patients with primary headache disorders and the sleep deprivation precipitates the migraine attacks. Also, RLS patients feruquently expeirence sleep problems.<sup>40,41</sup> Association of migraine with RLS might be a causation. Therefore, dopaminergic therapy of RLS may either provide migraine control by improvement of the sleep or

induce the migraine attacks by dopaminergic system effect explained above.

Both migraine and RLS found to be related with mood disorders and mood disorders might be related to sleep disturbances.<sup>42,43</sup> In our study, we did not evaluate neither depressive nor anxiety disorders, so we cannot exclude the sleep problems connected to psychiatric etiology in our participants. However, this study is not designed to confirm the psychiatric comorbidities, it may be a subject for another study.

Another limitation of our study is the number of our participants between groups were not equally distrubated, this might be affected our statistical analysis. And we did not questioned the temporality between migraine and RLS.

Despite the weaknesses, our study demonstrates an association between RLS and migraine, and it also reflects that sleep disturbances and caffeine intake contribute this association. Although the study was not designed as population based, we believe that it reflects the characteristic of young population.

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