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ARAŞTIRMA / RESEARCH

Relationship of restless legs syndrome with blood parameters

Huzursuz bacak sendromunun kan parametreleri ile olan ilişkisi

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Abstract

Purpose: We aimed to investigate the factors affecting the etiopathogenesis by comparing the restless legs syndrome patients with the healthy control group in terms of some laboratory parameters.

Materials and Methods: Patients who were diagnosed with restless legs syndrome were included in the study. A control group that was similar in terms of age and gender was formed. Both groups were compared in terms of iron, ferritin, iron-binding capacity, folate, vitamin B12, vitamin D, calcium, magnesium, ALT, AST, hemogram, creatinine, fasting blood sugar, and thyroid hormone levels.

Results: 37 patients with restless legs syndrome and 41 controls were included in the study. In the restless legs syndrome group hemoglobin, ferritin, iron, fasting blood sugar, vitamin D, and fT4 values were 12.7 (10.3-16.0) g/dL, 37.3 (3.7-89.4) mg/L, 62 (21-195) µg/dL, 96 (65-250) mg/L, 11.26 (4.20-41.57) ug/L and 1.24 (0.73-2.14) µg/dL respectively, they were 14.8 (12.3-16.1) g/dL, 56 (9-189) mg/L, 90 (30-245) µg/dL, 91 (70-107) mg/L, 17.31 (5.73-32.90) µg/L and 1.08 (0.63-2.04) µg/dL respectively in the control group.There were statistically significant differences between the groups in terms of hemoglobin, ferritin, iron, fasting blood sugar, vitamin D, and fT4 levels.

Conclusion: Hemoglobin and iron parameters, vitamin D levels, fasting blood sugar and T4 levels should be evaluated in patients with restless legs syndrome and should be replaced if necessary. Correction of deficiencies may be beneficial for patients' clinics.

Keywords:. Restless legs syndrome, iron parameters, vitamin D

Öz

Amaç: Bu çalışma ile, huzursuz bacak sendromlu hastaları, sağlıklı kontrol grubu ile bazı laboratuvar parametreleri açısından karşılaştırarak etyopatogenezi etkileyen faktörleri araştırmak amaçlanmıştır.

Gereç ve Yöntem: Huzursuz bacak sendromu tanısı konulan hastalar çalışmaya dahil edildi. Yaş ve cinsiyet açısından benzer kontrol grubu oluşturuldu. Her iki grup demir, ferritin, demir bağlama kapasitesi, folat, vitamin B12, vitamin D, kalsiyum, magnezyum, ALT, AST, hemogram, kreatinin, açlık kan şekeri, tiroid hormon seviyeleri açısından karşılaştırıldı.

Bulgular: Çalışmaya 37 huzursuz bacak sendromu hastası, 41 tane de kontrol dahil edildi. Huzursuz bacak sendromu grubunda hemoglobin, ferritin, demir, açlık kan şekeri, D vitamini ve fT4 değerleri sırasıyla 12.7 (10.3-16.0) g/dL, 37.3 (3.7-89.4) mg/L, 62 (21-195) µg/dL, 96 (65-250) mg/L, 11.26 (4.20-41.57) ug/L ve 1.24 (0.73-2.14) µg/dL iken kontrol grubunda sırasıyla 14.8 (12.3-16.1) g/dL, 56 (9-189) mg/L, 90 (30-245) µg/dL, 91 (70-107) mg/L, 17.31 (5.73-32.90) µg/L ve 1.08 (0.63-2.04) µg/dL idi. Hemoglobin, ferritin, demir, açlık kan şekeri, vitamin D ve T4 seviyeleri açısından gruplar arasında istatistiksel olarak anlamlı farklılıklar saptandı.

Sonuç: Huzursuz bacak sendromlu hastalarda hemoglobin ve demir parametreleri, vitamin D düzeyleri, açlık kan şekeri ve T4 seviyeleri eksiklikleri açısından mutlaka değerlendirilmeli, gereklilik halinde mutalaka replase edilmelidir. Eksikliklerin düzeltilmesi hastaların klinikleri açısından yararlı olabilir.

Anahtar kelimeler: Huzursuz bacak sendromu, demir parametreleri, D vitamini

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INTRODUCTION

Restless Legs Syndrome (RLS) is a common movement disorder characterized by a feeling of discomfort in the legs and sometimes an uncontrollable sudden need to move due to pain. It is characterized by a feeling of restlessness and discomfort in the legs (rarely in the arms), paresthesias, and an irresistible urge to move. Symptoms often occur in the evening and at night, especially when at rest. Moving causes the complaints to decrease or disappear[1]. The frequency of RLS varies between 3-10% in the general population. In Asian countries, this rate drops to 1.8%[2]. There are two forms of the disease: primary (idiopathic) RLS and secondary (symptomatic) RLS. The primary form includes genetic reasons and etiological causes of unknown origin. Family history is 50% positive in primary RLS. The secondary form can have a wide variety of causes. Iron deficiency, terminal stage renal failure, Parkinson's disease, polyneuropathy, pregnancy, and drugs are the leading causes. Antiemetics, antipsychotics, antihistamines, some antiepileptics, as well as antidepressants can cause or exacerbate RLS[3]. Physical examination is often normal, except for findings that may be specific to the secondary form. It has been reported in the literature that RLS symptoms are caused by local iron deficiency or dopamine dysfunction in the central nervous system. Pharmacological treatment should be considered in cases of deterioration in the person's sleep or quality of life and is based on relief of symptoms. In treatment, dopaminergic agents, ergot derivatives, and dopamine receptor agonists may be preferred[4].

Although the association of diseases such as iron deficiency, pregnancy, and chronic renal failure (CRF) with RLS has been extensively studied in the literature, the number of studies examining the relationship between vitamin D, thyroid function tests, and other laboratory parameters is limited. In this study, we hypothesized that there may be other etiological features associated with RLS apart from the previously investigated parameters. Accordingly, we hypothesized that vitamin D, thyroid function tests, vitamin B12 and other different parameters might be associated with RLS. Thus, we wanted to pave the way for studies that can provide positive improvement in the treatment and clinical condition of patients by correcting the related parameters that we will determine.

Our purpose with this study is to investigate the factors affecting the etiopathogenesis by comparing the RLS patients with the healthy control group in terms of some laboratory parameters.

MATERIALS AND METHODS

Sample

Patients over the age of 18 who applied to Hatay Mustafa Kemal University Health Practice and Research Hospital Neurology outpatient clinic between 2018 and 2021 and were diagnosed with RLS were retrospectively scanned and recorded. Patient records and investigated parameters were safely obtained retrospectively using the Hospital Information Management System – Enlil. The patients were diagnosed with RLS using the diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[5]. Accordingly, patients who met all 5 diagnostic criteria were diagnosed with RLS.

These diagnostic criteria are: 1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs. 2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting. 3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. 4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day. 5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)[5].

Diseases that may cause RLS-like complaints were accepted as exclusion criteria because they may cause diagnostic confusion. Also, patients who received treatment related to the investigated parameters were excluded from the study as it may cause incorrect correlation results. Thus, vascular diseases of the lower extremity, attention deficit, and hyperactivity disorder, painful legs and moving toes syndrome, cerebral or spinal cord injuries, chronic inflammatory diseases, receiving iron replacement therapy during the evaluation, pregnancy, and malignancy were

accepted as exclusion criteria from the study. A control group was formed from participants of similar age and gender who applied with headache complaints between 2018-2021 and did not have any additional disease.

This study was approved by the Clinical Study Ethics Committee of Mustafa Kemal University Tayfur Ata Sökmen Medical Faculty (Approval no:03/32, Date:17/03/2022).

Procedure

Iron, ferritin, iron-binding capacity, folate, vitamin B12, vitamin D, calcium, magnesium, ALT, AST, hemogram, creatinine, fasting blood sugar, and thyroid hormone levels of both groups were scanned and recorded retrospectively from the registry system. Both groups were compared in terms of these parameters. Reference values were not given because values outside or within the normal range were not evaluated, only the control group and patient group were compared.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 22.0 program was used to evaluate the data obtained from the study. All study data were evaluated by a statistician. Normal distribution conformity of continuous numerical variables was analyzed with the Shapiro Wilk test (n<50). All data were given as mean ± standard deviation, median (minimum-maximum) number, and percentage (%). Chi-square test was used to compare the percentages of categorical variables between groups. The Independent Sample T-Test was used to compare normally distributed measurements between groups, and the Mann-Whitney U test was used to compare non-normally distributed measurements between groups. Spearman correlation analysis was used to measure the relationship between numerical variables. The correlation coefficient (r) was considered as follows: weak; between 0.000-0.249; medium; between 0.250-0.499; strong; between 0.500-0.749 and very strong; between 0.750-1,000. The p-value of <0.05 was considered significant according to statistical tests.

RESULTS

The study group consisted of 78 participants. The RLS group consisted of 37 patients and the control group consisted of 41 healthy participants. Of 37 RLS patients, 28 (75.7%) were female and 9 (24.3%) were male. Of 41 healthy volunteers, 31 (75.6%) were female and 10 (24.2%) were male. The mean age in the RLS group was 48.40 ± 12.62 years. It was 46.90 ± 11.01 years in the control group. There was no statistical difference between the two groups in terms of age and gender (respectively; p=0.995, p=0.576, Table 1).

Table 1. Comparison of demographic characteristics between groups

Variables	RLS (n=37)	Control (n=41)	P
Gender (n/%)			
Female	28 (75.7)	31 (75.6)	0.995*
Male	9 (24.3)	10 (24.4)	
Age (year) (mean ± SD)	48.40 ± 12.62	46.90 ± 11.01	0.576**

n: number, SD: Standard Deviation, * Chi-square Test, **Independent Sample T-Test

The comparison of hemogram, biochemistry, and hormonal data of individuals included in the study between groups is given in Table 2.

While the median value of hemoglobin level in the RLS group was 12.7 (10.3-16.0) g/dL, it was 14.8 (12.3-16.1) g/dL in the control group. The median value of ferritin level was 37.3 (3.7-89.4) mg/L in the RLS group and 56 (9-189) mg/L in the control group. The median iron level was 62 (21-195) µg/dL in the RLS group, and it was 90 (30-245) µg/dL in the control group. We found a statistically significant difference between the two groups in terms of hemoglobin, ferritin, and iron levels. (Respectively; p=0.000, p=0.014, p=0.000). The median value of fasting blood sugar level was 96 (65-250) mg/L in the RLS group, it was 91 (70-107) mg/L in the control group. We found a statistically significant difference between both groups in terms of fasting blood sugar (p=0.043).

The mean calcium level in the RLS group was 9.26 ± 0.54 mg/L, it was 9.31 ± 0.49 mg/L in the control group. The mean magnesium level in the RLS group

was 1.99 ± 0.24 mg/L, and it was 2.03 ± 0.23 mg/L in the control group. There was no statistically significant difference between the two groups in terms of calcium and magnesium levels (Respectively; p=0.693, p=0.481). The median value of vitamin D level in the RLS group was 11.26 (4.20-41.57) ug/L, and it was 17.31 (5.73-32.90) ug/L in the control group. We found a statistically significant difference between both groups in terms of vitamin D levels (p=0.000).

The median value of vitamin B12 level in the RLS group was 330 (132-694) pg/mL, it was 343 (231-698) pg/mL in the control group. The median value of folate level was 9.68 (4.71-28.00) ng/mL in the RLS group, and it was 9.12 (1.93-26.00) ng/mL in the control group. The median value of creatinine level was 0.69 (0.41-7.73) mg/dL in the RLS group, it was 0.69 (0.38-1.04) mg/dL in the control group. We did not find a statistically significant difference between the two groups in terms of B12, folate, and creatinine levels (Respectively; p=0.296, p=0.387, p=0.830).

The median value of TSH level was 1.59 (0.01-5.98) μIU/mL in the RLS group, it was 1.68 (0.57-3.08) μIU/mL in the control group. The median value of T3 level in the RLS group was 3.02 (1.87-3.54) ug/dL, and it was 3.13 (1.92-4.49) ug/dL in the control group. The median value of T4 level in the RLS group was 1.24 (0.73-2.14) ug/dL, it was 1.08 (0.63-2.04) ug/dL in the control group. While there was no statistically significant difference between the groups in terms of TSH and T3 values, there was in terms of T4 values (Respectively; p=0.222, p=0.113, p=0.003). When we examine RLS patients in terms of concomitant diseases, 8 of them had diabetes mellitus (DM), 2 had a CRF, 3 had hyperthyroidism, and 1 had hypothyroidism.

Table 2. Comparison of hemogram, biochemical and hormonal data between groups

Variables	Group	n (number)	Mean ± SD Median (Min-Max)	*P*
Hemoglobin (g/dL)	RLS	37	12.7 (10.3-16.0)	0.000*
	Control	41	14.8 (12.3-16.1)	
Ferritin (mg/L)	RLS	37	37.3 (3.7-89.4)	0.014*
	Control	41	56 (9-189)	
Iron (μg/dL)	RLS	37	62 (21-195)	0.000*
	Control	41	90 (30-245)	
Fasting blood sugar (mg/dL)	RLS	37	96 (65-250)	0.043*
	Control	41	91 (70-107)	
Ca (mg/dL)	RLS	37	9.26 ± 0.54	0.693**
	Control	41	9.31 ± 0.49	
Mg (mg/dL)	RLS	37	1.99 ± 0.24	0.481**
	Control	41	2.03 ± 0.23	
Vitamin D (ug/L)	RLS	37	11.26 (4.20-41.57)	0.000*
	Control	41	17.31 (5.73-32.90)	
Vitamin B12 (pg/mL)	RLS	37	330 (132-694)	0.296*
	Control	41	343 (231-698)	
TSH (μIU/mL)	RLS	37	1.59 (0.01-5.98)	0.222*
	Control	41	1.68 (0.57-3.08)	
T3 (ug/dL)	RLS	37	3.02 (1.87-3.54)	0.113*
	Control	41	3.13 (1.92-4.49)	
T4 (ug/dL)	RLS	37	1.24 (0.73-2.14)	0.003*
	Control	41	1.08 (0.63-2.04)	
Folate (ng/mL)	RLS	37	9.68 (4.71-28.00)	0.387*
	Control	41	9.12 (1.93-26.00)	
Creatinine (mg/dL)	RLS	37	0.69 (0.41-7.73)	0.830*
	Control	41	0.69 (0.38-1.04)	

SD: Standard Deviation, Min: Minimum, Max: Maximum, Ca: Calcium, Mg: Magnesium, TSH: Thyroid Stimulating Hormone, T3: Thyriodothyronine, T4: Thyroxine, * Mann-Whitney U Test, ** Independent Sample T-Test

DISCUSSION

In our study, we found hemoglobin, ferritin, and iron levels to be statistically significantly lower in the patient group than in the control group. The median value of fasting blood sugar was higher in the patient group. There was no statistically significant difference between the groups in terms of calcium and magnesium levels. Vitamin D level was found to be statistically significantly lower in the patient group compared to the control group. There was no significant difference between the groups in terms of B12, folate, and creatinine levels. In terms of thyroid parameters, only T4 values were found to be higher in the patient group. The most common comorbidities in the patient group were diabetes mellitus, CRF, hyperthyroidism, and hypothyroidism.

37 RLS patients were included in the study. 28 (75.6%) of these patients were women. In most of the studies examining the relationship between RLS and gender, it was reported that the prevalence was higher in women than in men. Again, in some studies, it has been reported that this rate is 2–3.5 times higher in women than in men[6, 7]. Consistent with the literature in our study, the prevalence of women was approximately 3 times that of men (75.6% vs. 24.4%). The reason for this is; It can be said that iron deficiency is more common in women and that the estrogen-progesterone cycle causes changes in metabolic pathways. Iron metabolism is very important in the pathophysiology of RLS[8].

The relationship between age and RLS is unclear in the literature. Some studies report that RLS increases with age[9]. However, many studies are reporting that the prevalence does not increase with age[10].

Karl Ekbom, who was one of the first to emphasize the relationship between iron and RLS, and who conducted studies on this, showed that serum iron level was low in 25% of cases with severe RLS in 1960[11]. In another study, iron deficiency was found in 43% of patients with RLS[12]. In another study, the severity of RLS symptoms was correlated with serum ferritin level[13]. The rate-limiting enzyme in dopamine production is Tyrosine hydroxylase, which requires iron as a cofactor. Therefore, iron deficiency causes an indirect decrease in dopamine production[14]. The majority of the iron in the brain is found in ferritin, which acts as a storage for intracellular iron. It has been reported that regional iron distribution in the brain is not homogeneous in healthy individuals and is more intense in the substantia nigra, deep cerebellar nucleus, corpus striatum, and red nuclei. Autopsy studies have shown that iron is decreased in the basal ganglia, which is the main center of dopamine metabolism in RLS[15]. In our study, iron and related parameters, ferritin and hemoglobin levels, were found to be lower than the control group. In addition, this low was found to be statistically significant.

The frequency of RLS in patients with type 2 diabetes mellitus has been reported between 17.7% and 28.6% in the literatüre[4]. Additionally, in a meta-analysis that included 644,506 patients in eight prospective observational studies, the prevalence of DM was found to be significantly higher in RLS patients than in the control group[16]. In our study, 8 (21.6%) of 37 RLS patients had DM. When we compared RLS patients with the control group in terms of fasting blood sugar, we find a statistically significant difference.

The role of vitamin D, which is an important prohormone in the regulation of dopaminergic system functions, in the pathophysiology of RLS is still unknown[16]. Studies have also shown that vitamin D exerts a neuroprotective effect by influencing the nigrostriatal dopaminergic pathways, causing an increase in dopamine and dopamine metabolites. Therefore, it is thought that the deficiency of vitamin D and its metabolites may lead to dopaminergic dysfunction and, as a result, to the formation of RLS[17]. The relationship between vitamin D deficiency and disease severity has also been demonstrated. In the study of Arife Çimen Atalar, when the severity of RLS was compared between patients with normal and low 25 (OH) vitamin D levels, the severity of the disease was found to increase more significantly in the group with low 25 (OH) vitamin D[18]. In our study, we found a statistically significant difference between the vitamin D levels of the two groups and there was no statistically significant difference between the two groups in terms of Ca and MG levels.

In the literature, mean vitamin B12, folate, and creatinine levels were similar in individuals with and without RLS[19]. Also in our study consistent with the literature, there was no statistically significant difference between the vitamin B12, folate, and creatinine levels of the two groups.

Thyroid hormones and central nervous system development are closely related. Investigating thyroid dysfunction in RLS may be useful to understand the

underlying pathogenesis of RLS. The relationship between thyroid hormone levels (TSH, T4, T3) and RLS has not been studied much in the literature. Gunes Aygul. et al., in their study, found that the rate of RLS was 38% in the hypothyroidism group and 13% in the hyperthyroidism group. They did not diagnose RLS in the healthy-volunteers group. In our study, no statistically significant difference was found between the TSH and T3 levels of the two groups. But, the median value of T4 level in the RLS group was 1.24 (0.73-2.14) ug/dL, while it was 1.08 (0.63-2.04) ug/dL in the control group. A statistically significant difference was found between the T4 levels of the two groups (p=0.003). However, much more studies are needed to reveal the relationship between thyroid hormone levels and RLS.

Since RLS is not a very common disease, the literature is limited to its relationship with pregnancy, iron parameters and kidney failure. There are few studies in the literature investigating the relationship between RLS and vitamin D, thyroid hormones and other laboratory parameters. We can say that we contributed to the relationship between the parameters we investigated in our study and RLS. We have shown that it is important to investigate these parameters in patients presenting with RLS.

The limitations of the study are its retrospective nature, small sample size, lack of association between the investigated parameters and disease severity, lack of power analyse to determine the number of samples and not investigating the effect of the corrected parameters on the treatment.

In conclusion, RLS is one of the most common neurological diseases that should be well known by physicians, especially neurologists because it accompanies many medical diseases. The etiopathogenesis of the disease has not been elucidated yet. There are few studies in the literature investigating the relationship between RLS and vitamin D, thyroid hormones and other laboratory parameters. Our study showed that laboratory characteristics such as iron parameters and vitamin D levels may often be low in RLS patients, and physicians should be vigilant in this regard. We would like to emphasize that better clinical results can be obtained in the treatment of RLS with the correction of accompanying factors. Along with the correction of these related factors, the investigation of the changes in the clinical status of the patients should be the subject of future studies.

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REFERENCES

1. Klingelhoefer L, Bhattacharya K, Reichmann H. Restless legs syndrome. Clin Med. 2016;16:379.
2. Zintzaras E, Kitsios GD, Papathanasiou AA, Konitsiotis S, Miligkos M, Rodopoulou P et al. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. Clin Ther. 2010;32:221-37.
3. Sayin S, Atilla FD. Demir eksikliğinin gözden kaçan klinik prezantasyonu; huzursuz bacak sendromu. Ankara Med J. 2019;19:694-7.
4. Üçgün AB, Kilit TP, Onbaşı K. Diyabetik hastalarda huzursuz bacak sendromu sıklığı ve ilişkili faktörlerin araştırılması. Prevalance. 2019;30:38.
5. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW et al. Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15:860-73.
6. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16:283-95.
7. Taşdemir M, Erdoğan H, Börü ÜT, Dilaver E, Kumaş A. Epidemiology of restless legs syndrome in Turkish adults on the western Black Sea coast of Turkey: A door-to-door study in a rural area. Sleep Med. 2010;11:82-6.

8. Sayin S, Atilla F. Overlooked clinical presentation of iron deficiency; restless Leg Syndrome. Ankara Med J. 2019:19-13.
9. Ulfberg J, Nyström B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord. 2001;16:1159-63.
10. Benediktsdottir B, Janson C, Lindberg E, Arnardóttir ES, Olafsson I, Cook E et al. Prevalence of restless legs syndrome among adults in Iceland and Sweden: lung function, comorbidity, ferritin, biomarkers and quality of life. Sleep Med. 2010;11:1043-8.
11. Ekbom K-A. Restless legs syndrome. Neurology. 1960;10:868-868.
12. Matthews W. Iron deficiency and restless legs. Br Med J. 1976;1:898.
13. O'keeffe S, Gavin K, Lavan J. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994;23:200-3.
14. Guo S, Huang J, Jiang H, Han C, Li J, Xu X et al. Restless legs syndrome: from pathophysiology to clinical diagnosis and management. Front Aging Neurosci. 2017;9:171.
15. Moon HJ, Chang Y, Lee YS, Song HJ, Chang HW, Ku J et al. T2 relaxometry using 3.0-tesla magnetic resonance imaging of the brain in early-and late-onset restless legs syndrome. J Clin Neurol. 2014;10:197-02.
16. Katsanos AH, Kosmidou M, Konitsiotis S, Tsivgoulis G, Fiolaki A, Kyritsis AP et al. Restless legs syndrome and cerebrovascular / cardiovascular events: systematic review and meta-analysis. Acta Neurol Scand. 2018;137:142-8.
17. Wali S, Shukr A, Boudal A, Alsaiari A, Krayem A. The effect of vitamin D supplements on the severity of restless legs syndrome. Sleep Breath. 2015;19:579-83.
18. Atalar AÇ. Huzursuz bacaklar sendromunda 25 (OH) vitamin d düzeylerinin hastalık şiddeti ve uyku kalitesi ile olan ilişkisi. Turk Noroloji Dergisi. 2019;25:87.
19. Högl B, Kiechl S, Willeit J, Saletu M, Frauscher B, Seppi K et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. Neurology. 2005;64:1920-4.