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Restless leg syndrome and migraine: Is there a common etiology?

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Abstract

Background & Objectives: Some studies have shown that there is a relationship between restless legs syndrome (RLS) and migraine. Our aim in this study is to investigate the relationship between RLS and migraine and the connection between their etiologies. *Methods:* This retrospective study was conducted on 109 RLS patients and 105 healthy individuals. Demographic parameters, migraine comorbidity, characteristics of RLS, as well as biochemical and hemogram parameters were examined in the study subjects. *Results:* The mean age of the RLS patients was 44.28±10.50 years and 38.84% suffered from migraine headaches. RLS was significantly more severe in patients with migraine. Compared to a control group of normal subjects, serum levels of vitamin D, calcium, and iron were significantly lower in RLS patients with or without migraine. The platelet counts, platelet-lymphocyte ratio (PLR), and C-reactive protein (CRP) levels were significantly higher in RLS patients without migraine compared to the control group ($p<0.05$)
Conclusion: RLS was more severe in patients with comorbid migraine. Vitamin D, calcium, and iron levels were significantly lower and inflammation markers were higher in all RLS patients. We think that further investigation of the underlying mechanisms of these two diseases and the results of population-based studies will enable clearer diagnosis and effective treatment of RLS and migraine in the future.

Keywords: Restless leg syndrome, migraine, iron deficiency, inflammation

INTRODUCTION

Restless leg syndrome (RLS) is characterized by unpleasant sensations in the leg. RLS sensations typically worsen at night and moving the legs relieves the discomfort. The prevalence of RLS ranges from 4% to 29% in North American and Western European Populations.[1] RLS can be categorized as primary (idiopathic) or secondary. Secondary RLS may coexist with various medical conditions such as diabetes, iron deficiency anemia, depression, anxiety, sleep disorders, Parkinson's disease, and kidney disease.[2] The pathophysiology of RLS is still partially understood. The most commonly accepted factors associated with RLS include genetic variants, abnormal iron metabolism, dopaminergic dysfunction, and the role of the central opioid system.[3]

Migraine is a common primary headache disorder that affects approximately 10% to 20% of the general population, predominantly women.[4] It presents primarily as unilateral, throbbing headache attacks that are responsive to movement and cause sensitivity to afferent inputs such as visual and auditory stimuli. Migraine significantly affects the quality of life during the peak productive years of an individual.[5] Studies show that many disorders such as anxiety and depressive disorders, cardiovascular disease, and pain disorders are associated with migraine.[6,7] Furthermore, it has been shown that the prevalence of RLS is higher in migraine patients compared to individuals without migraine.[8,9] A higher prevalence of migraine has also been reported in patients with RLS.[10,11]

The coexistence of RLS and migraine has led researchers to investigate common pathophysiological mechanisms in the etiology. It has been shown that hypothalamic dopaminergic A11 nucleus dysfunction may be involved in RLS. Conversely, dopamine has been shown to be associated with migraine symptoms such as yawning, food cravings, and gastrointestinal disturbances.[12,13] Similarly, changes in brain iron metabolism are observed in migraine patients

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and iron deficiency has been shown to be an important component in the pathophysiology of RLS.[14] Common factors to be determined in the etiology of RLS and migraine may guide the prevention and treatment of these diseases. In this study, we aimed to investigate the frequency of migraine in patients with RLS, the characteristics of RLS, and common biochemical parameters and inflammatory markers that may be involved in the etiology of both conditions. Therefore, we reviewed the studies dealing with this issue and attempted a more comprehensive evaluation of these issues.

METHODS

This retrospective study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2020-07/683). All study procedures were conducted in accordance with the principles of the Declaration of Helsinki. The study included 139 patients with the diagnosis of RLS who were admitted and followed up to the neurology and internal diseases outpatient clinic in the period between January 2019 and January 2021. Thirty patients were excluded from the study because they had non-migraine headaches. Patients with a diagnosis of RLS were classified according to whether they had migraine or not as RLSWM (RLS with migraine) and RLSWOM (RLS without migraine) groups, respectively. Patients with a history of chronic disease (diabetes, chronic diseases of the liver, kidney, heart, lungs, or the thyroid, or hematologic disorders), immunodeficiency, acute or chronic inflammatory diseases, oncological diseases, thalassemia; pregnant women, patients with a history of infection in the last month, and patients with a history of drug use were excluded. As the control group, 105 healthy individuals were included in the study. These had been seen at the outpatient clinic for check-ups and had no known diseases.

Demographic characteristics and the results of biochemistry tests, hemograms, erythrocyte sedimentation rates (ESR), and CRP levels of both the patient group and the control group were recorded. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, The platelet-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count, and the monocyte-HDL-cholesterol ratio (MHR) was obtained by dividing the number of monocytes by the level of HDL. NLR, PLR, and MHR ratios have been used as an inexpensive and easily calculated index to evaluate systemic inflammation in recent years.[15,16] It has been reported that NLR, PLR and MHR values may lead to diagnosis and prognosis in many systemic diseases such as malignancies, chronic inflammatory diseases, acute myocardial infarction, renal artery stenosis, diabetes mellitus.[17,18] These ratios were compared between the patient and control groups.

The diagnosis of RLS was made according to the criteria for restless legs syndrome and the diagnosis of migraine was made according to the criteria of the International Classification of Headache Disorders. RLS has 5 essential diagnostic criteria (Table 1).[5,19] The RLS Severity Rating Scale developed by the International RLS Working Group (IRLSSG) was administered to the patients diagnosed with RLS. The RLS Severity Rating Scale consists of 10 questions. The total score that can be obtained from the scale ranges from 0 to 40. A score of 1-10 indicates mild disease (Grade 1), 11-20 indicates moderate severity (Grade 2), 21-30 indicates severe disease (Grade 3), and 31-40 indicates very severe disease (Grade 4).[20] The patients were classified as lower extremity and lower+upper extremity involvement according to their clinical presentation.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics 23 package software. Frequencies (counts and percentages) and descriptive statistics (mean, standard deviation) were presented for categorical variables.

Numerical variables were analyzed by the Kolmogorov Smirnov normality test; which revealed that the variables were normally distributed. Because the assumption of normal distribution was confirmed, parametric statistical methods were used for statistical analysis. Differences between more than two independent groups were analyzed by One-Way Analysis of Variance (ANOVA). The Tukey multiple comparison test was used when a difference was detected by ANOVA. Relationships between two independent categorical variables were examined by the chi-square test. Statistical significance was evaluated at a value of 0.05.

RESULTS

The mean age was 44.28±10.50, 45.76±11.08, and 42.30±11.57 years in RLSWM, RLSWOM, and control groups, respectively. The results of ANOVA showed that the mean age was not

Table 1: 2012 revised RLS diagnostic criteria

Essential diagnostic criteria	
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 is 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).
Specifiers for clinical course of RLS	
A	Chronic-persistent RLS; Symptoms occurring at least twice a week on average for the past year when not treated.
B	Intermittent RLS; Symptoms occurring less than twice a week on average for the past year when not treated.
Specifiers for clinical significance of RLS	
The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact onsleep, energy/vitality, daily activities, behavior, cognition, or mood.	

different across groups (p>0.05). Of the patients with RLSWM, 29.4% were women and 14.8% were men. Of the patients with RLSWOM, 25.5% were women and 26.2% were men. (Table 2).

The results of the chi-square test showed that RLS severity was significantly different between the 3 groups (p<0.05). RLS was more severe when migraine was present. The frequency of patients with RLS severity of Grade 3-4 was significantly higher in the RLSWM patient group but there were significantly more patients with RLS severity of Grade 1 in the RLSWOM patient group (p=0.003). No statistically significant association of the coexistence of RLS and migraine was found with extremity involvement (p>0.05) (Table 2). There was no statistically significant relationship between the distribution of extremity involvement and the coexistence of RLS and migraine (p>0.05) (Table 3).

There was a statistically significant difference in the levels of vitamin D, calcium, iron, ferritin, and total iron binding capacity (TIBC) across the groups (p<0.05). The levels of vitamin D, calcium, and iron levels were statistically lower in the RLSWM and RLSWOM groups compared to the control group. In the RLSWM group, ferritin levels were significantly lower and the TIBC levels were significantly higher compared to the

Table 2: Demographic characteristics of patients by groups

	RLSWM (n=54) Mean±SD	**RLSWM (n=55) Mean±SD**	**Controls (n=105) Mean±SD**	**F**	**p**
Age (years)	44.28±10.50	45.76±11.08	42.30±11.57	1.826	0.164
	n(%)	**n(%)**	**n(%)**	Chi-square	
Gender					
Women	45(29.4)	39(25.5)	69(45.1)	5.444	0.066
Men	9(14.8)	16(26.2)	36(59.0)		

F: One-way analysis of variance (ANOVA), RLSWM: Restless leg syndrome with migraine, RLSWOM: Restless leg syndrome without migraine

Table 3: Clinical features of RLS

	RLSWM (n=54) Mean±SD	RLSWOM (n=55) Mean±SD	Chi-Square	p
Severity				
Grade 1	**9±16.7**	**25±45.5**	11.752	**0.003***
Grade 2	21±38.9	18±32.7		
Garde 3 and 4	**24±44.4**	**12±21.8**		
Extremity Involvement				
Lower	39±72.2	42±76.4	0.245	0.621
Lower+Upper	15±27.8	13±23.6		

*: p<0,05. SD: Standard deviation. RLSWM: Restless legs syndrome with migraine, RLSWOM: Restless legs syndrome without migraine

control group (p=0.008, p=0.000) (Table 4).

There was a statistically significant difference in platelet counts, PLR, and the levels of HDL, sedimentation, and CRP across the groups (p<0.05). The platelet count, PLR, and CRP levels were significantly higher in RLSWOM patients compared to the control group. Although HDL levels of the control group were significantly higher than those of RLSWM and RLSWOM groups, MHR was not significantly different across groups. Sedimentation levels of RLSWM and RLSWOM patients were significantly higher than the individuals in the control group (p=0.000) (Table 5).

DISCUSSION

Migraine and RLS are common diseases that predominantly affect women.[21,22] Gupta *et al*. found a 51.5% rate of headache in RLS patients; 44.4% of which were diagnosed with migraine.[11] Similarly, in our study, 38.84% of RLS patients had migraine headaches. In our study, the mean age of RLSWM patients was 44.28±10.50 years and 83% were women. Gozubatik *et al*. found out that the mean age of RLS patients was 50.4 ± 12.8 years and 67.5% of patients with comorbid migraine were women.[10]

Studies have shown that the prevalence and severity of RLS increases with advancing age as well as with coexistent mood disorders and sleep impairment.[23-25] Rhode *et al*. found that the RLS severity scale scores were higher in patients having both RLS and migraine than in RLS without migraine, but a statistically significant difference was not detected.[26] In our study, the severity of RLS was significantly higher in RLS patients with migraine. However, in some studies, no association of the severity of RLS was observed with migraine and other primary headaches.[11,27] In our study, all patients (n=109) had lower extremity involvement and 25% (n=28) of the patients had both upper and lower extremity involvement. Similarly, in the study of Yeh *et al*., all patients (n=122) had RLS complaints in their legs and 35% of patients had both upper and lower extremity involvement.[28] Although a

Table 4: Biochemical test results and differences by groups

	RLSWM (n=54) Mean±SD	RLSWOM (n=55) Mean±SD	Controls (n=105) Mean±SD	F	p	Differences
Vit D (ng/ml)	14.72±5.01	15.17±7.54	17.93±7.01	5.351	**0.005***	**3-1.2**
Ca (mg/dL)	9.38±0.40	9.38±0.44	9.89±0.36	43.404	**0.000***	**3-1.2**
Mg (mg/dl)	2.00±0.17	2.01±0.16	2.02±0.16	0.258	0.773	-
Iron (ug/dl)	67.1±39.9	74.1±31.9	102.2±41.8	17.900	**0.000***	**3-1.2**
Ferritin (ng/ml)	30.3±26.7	56.6±68.7	61.7±67.8	4.981	**0.008***	**1-3**
TIBC (ug/dl)	389.0±59.3	365.1±78.6	350.8±62.6	5.956	**0.003***	**1-3**
B12 (pg/mL)	298.0±88.8	331.2±119.6	329.2±114.8	1.695	0.186	-

F: One-way analysis of variance (ANOVA), *: p<0.05. RLSWM: Restless legs syndrome with migraine, RLSWOM: Restless legs syndrome without migraine, D vit: vitamin D, Ca: Calcium, Mg: Magnesium, TIBC: total iron binding capacity, B12: vitamin B12

Table 5: Differences in hematologic parameters, ESR, and CRP and HDL levels by groups

	RLSWM (n=54) Avg ± SD	RLSWOM (n=55) Avg ± SD	Controls (n=105) Avg ± S.D.	F	p	Difference
WBC (×10³ µl)	6.70±1.52	7.04±1.58	6.84±1.62	0.641	0.528	
PLT (×10³ µl)	266.4±69.0	281.2±65.7	252.8±54.5	3.951	**0.021***	**2-3**
LYM (×10³ µl)	2.85±3.06	2.41±0.69	4.15±6.96	2.466	0.087	
NEU (×10³ µl)	3.45±1.12	3.83±1.28	4.19±5.20	0.705	0.495	
MON (×10³ µl)	0.47±0.18	0.47±0.21	0.54±0.97	0.270	0.763	
HDL (mg/dl)	49.7±11.9	48.3±12.7	56.2±10.4	10.813	**0.000***	**3-1.2**
NLR	1.49±0.68	1.75±0.94	1.52±0.63	2.180	0.116	
PLR	115.21±41.81	127.48±51.03	105.56±43.97	4.256	**0.015***	**2-3**
MHR	0.01±0.00	0.01±0.01	0.01±0.02	0.028	0.972	
ESR (mm/l)	16.7±9.5	13.9±7.2	6.9±3.6	46.761	**0.000***	**3-1.2**
CRP (mg/l)	0.40±0.63	0.67±1.96	0.16±0.18	4.328	**0.014***	**2-3**
Hb (g/dl)	13.08±1.91	13.46±2.17	15.92±12.82	2.270	0.106	

F: One-way analysis of variance (ANOVA), *: p<0.05, RLSWM: Restless legs syndrome with migraine, RLSWOM: Restless legs syndrome without migraine. WBC: white blood cell, PLT: platelets, LYM: lymphocytes, NEU: neutrophils, MON: monocytes, HDL: high-density lipoprotein, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MHR: monocyte/HDL ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin

relationship was found between the severity of RLS and upper extremity involvement in several previous studies, a significant relationship was not found in our study.[29,30]

Studies in the literature show that the dopaminergic system plays an important role in the pathophysiology of RLS.[31] It has been reported that vitamin D acts on the nigrostriatal dopaminergic pathway by increasing the levels of dopamine or its metabolites and protecting dopaminergic neurons against toxins.[32] In patients with migraine, it has been suggested that vitamin D deficiency aggravates neuroinflammation and that the neuronal hypersensitivity in hypocalcemia may increase the severity of migraine attacks by contributing to sensory symptoms of migraine.[33,34] In our study, the levels of vitamin D, calcium, and iron were significantly lower in patients with RLSWM and RLSWOM compared to the control group. Similarly, Wali *et al*. showed that vitamin D and ferritin values of patients with RLS were significantly lower than those of the control group.[35] In another study, hypocalcemia and vitamin D deficiency were found to be associated with migraine attacks and loss of function in migraine.[36]

Iron deficiency affects many cellular functions and processes including oxygen delivery, electron storage and transport, oxidative phosphorylation, neurotransmitter metabolism, immune function, and DNA synthesis.[37] Previous studies have shown that RLS is associated with iron deficiency anemia and that the symptom severity in RLS is associated with serum ferritin levels.[14,38] Furthermore, it has been shown that iron plays an important role in the synthesis of serotonin, dopamine, and norepinephrine, and that serotonin levels are associated with migraine.[39,40] In our study, the iron levels of the patients with RLS were found to be lower than those of the control group. In the RLSWM group, ferritin levels were lower and TIBC was higher. The presence of more severe iron deficiency and more severe RLS in patients with RLSWM suggests the presence of a common etiology.

The inflammatory or infectious character of the factors that have been associated with RLS suggests that systemic inflammation has an etiological role to play.[41] In the migraine pathogenesis, neurogenic inflammation is involved along with the contribution of oxidative stress, cytokines, and vasomotor changes.[42] In our study, sedimentation levels were found to be significantly higher in all patients with RLS compared to the control group. Yazar *et al*. found a higher neutrophil count and NLR, PLR, and MLR values in migraine patients compared to the control group.[43] In another study, Varım *et al*. found a significantly higher NLR value in patients with RLS.[44] In our study, the platelet

count, PLR, and CRP levels were higher in the RLSWOM group compared to the control group.

In conclusion, we have shown in our study that migraine occurs at significantly higher rates in patients with RLS. We found that RLS was more severe in patients having concurrent RLS and migraine. We found that the levels of vitamin D, calcium, and iron were significantly lower and inflammation markers were higher in all patients diagnosed with RLS. In the group with RLS and migraine, iron deficiency and RLS were more severe compared to the RLS group without migraine. These results provide important information about the common points in the physiopathology of RLS and migraine. We think that further investigation of the underlying mechanisms of both diseases and the results of population-based studies will enable more effective diagnosis and treatment of these diseases in the future.

DISCLOSURE

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