Restless legs syndrome in migraine patients at an outpatient clinic

Ayşe Çağlar Sarılar[1], Büşra S. Arıca Polat[2], Nesrin Karahan[3], Muhittin Cenk Akbostancı[4]

[1]Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey

[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Neurology, Ankara, Turkey

[3]Gazi Mustafa Kemal State Hospital, Clinic of Neurology, Ankara, Turkey

[4]Ankara University Faculty of Medicine, Department of Neurology, Ankara, Turkey

Corresponding Author:
Büşra S. Arıca Polat, M.D., University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Neurology, Ankara, Turkey
busrarica@yahoo.com

ORCID:
orcid.org/0000-0001-7818-1209

ABSTRACT

Aims: The prevalence of Restless legs syndrome (RLS) in migraine patients is estimated to be 8.7-39.0%. In this study, we set out to compare the frequency of RLS in patients diagnosed with migraine with headache free participants.

Methods: We included 201 patients with migraine with or without aura and age and gender-matched 102 headache free group from outpatient setting in this cross-sectional study. None of the migraine patients were receiving prophylactic medications that could affect dopamine metabolism. Patients with comorbidities such as kidney disease, Parkinson's disease, rheumatoid arthritis, and polyneuropathy were excluded from this study. The headache free participants had no neurological or systemic disease, no addiction/and no medical treatment. The frequency and severity (with RLS Rating Scale) of RLS was examined in two groups.

Results: 40.3% (n=81) of the migraine patients met the diagnostic criteria for RLS than the headaches-free participants (15.7%, n=16) (p<0.001). The RLS (+) and RLS (-) migraine groups were similar in terms of age, gender, number of attacks per month, presence of aura, smoking, and family history for RLS. Disease duration was longer in the migraine patients with RLS and RLS severity was higher in patients with longer disease duration (p<0.001 and p=0.05). Five of six patients with hypertension and migraine patients had RLS (vs. 76 of 195 for patients without hypertension, p=0.04). Logistic regression analysis showed a significant association only between the disease duration and the presence of RLS [Odds ratio: 13.25, (95% confidence interval: 5.62-31.24), p=0.001].

Conclusions: This study found almost three times higher frequency of RLS in patients with migraine. RLS symptoms should be questioned during the management of patients with a migraine diagnosis, particularly in long-standing disease.

Introduction

Migraine is a chronic headache syndrome that lasts 4-72 hours, usually unilateral, throbbing, moderate or severe, and characterized by recurrent attacks that increases with routine physical activities associated with nausea and/or vomiting or photophobia, phonophobia (1). It is 2.5 times more likely in women than men, and its prevalence in Turkey is 16.4% (2).

Restless legs syndrome (RLS) is defined as the feeling of restlessness in the legs, rarely in the arms, or the desire to move the legs, which worsens in long-term inactivity especially at night, and improves with movement (3). In studies using different methods, the worldwide prevalence of RLS has been reported as 2.5-29% (4). In our country, this rate is between 5.52-9.7% according to the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria and it is seen twice as often in women (5-7). There are clinical and epidemiological studies show that there is a relationship between migraine and RLS (8). Both the frequency of RLS in patients with migraine and the frequency of migraine in patients with RLS is higher than

in controls (9). The prevalence of RLS in migraine patients is estimated to be 8.7-39.0% (3,10). This association is thought to be related to a common pathophysiological link rather than comorbidity (11). The most common reason for this association may be dopamine and iron metabolism disorders. However, the etiopathogenesis of RLS and its relationship and/or comorbidity with migraine has not been clarified yet.

To the best of our knowledge, only one study was published on the prevalence of RLS in Turkish migraineurs, and it was reported that the frequency of RLS was higher than controls (12). The authors observed association of RLS with the age of the patient and duration of the disease. To contribute the existing literature and improve the in the field, we aimed in this study to compare the frequency of RLS in patients diagnosed with migraine and

Headache-free controls. We also explored the clinical characteristics of migraine patients with RLS.

Methods

Migraine patients and headache-free participants

This cross-sectional study included patients admitted to the neurology outpatient clinic and were diagnosed with migraine with or without aura according to The International Classification of Headache Disorders-III. The control group included age and gender-mathced headache free volunteers (1). The headache free group did not have any neurological or systemic disease, addiction or medical treatment. The study group and headache-free controls were evaluated by two neurologists and detailed neurological were examined. None of the migraine patients were receiving prophylactic medications such as serotonin reuptake inhibitors or amitriptyline that could affect dopamine metabolism. Age, gender, average number of migraine attacks per month, length of disease, the presence of aura, a type of aura, coexistening of hypertension, smoking, family history for RLS were recorded. Patients with comorbidities such as kidney disease, Parkinson's disease, rheumatoid arthritis, and polyneuropathy were excluded. Hemoglobin (Hb) level above 13.0 g/dL for men and 12.0 g/dL for women, and serum ferritin level above 50 mL/ng were taken as reference values (13).

All procedures were performed in accordance with the Declaration of Helsinki, Erciyes University Clinical Research Local Ethics Committee (decision no: 2021/147, date: 03.03.2021), and informed written consent was obtained from all participants or their legal representatives.

Clinical evaluation

RLS was diagnosed using the IRLSSG criteria in migraine patients and headache-free participants by two neurologists using face-to-face interview. The IRLSSG diagnostic criteria include five-questions based on the patient's history (5). Subjects who met all RLS diagnostic criteria were accepted as RLS (+). Then, the Turkish version of "RLS Rating Scale" was applied to the patients diagnosed with RLS (14). This scale consists of 10 questions each graded between 0 and 4. While the first five questions are related to the severity of symptoms, and the last five questions are related to the effects of RLS on daily living activities or quality of life. The score obtained indicates the severity of the disease. The highest score in this tool is 40, and while scores between 1 and 10 are classified as mild, between 11 and 20 moderate, between 21 and 30 severe, and between 31 and 40 very severe.

Statistical Analysis

We performed statistical analyses using the IBM Statistical Package for Social Sciences statistics 21.0 (IBM.Corp., Armonk, NY, 2012). Descriptive statistics were displayed as mean±standard deviation for continuous variables; and as counts and proportions for categorical data. The distribution normality of the continuous variables was calculated using the Shapiro-Wilk test. We used independent samples t-test to compare continuous variable fort he normally distributed variables and the chi-square test for categorical variables. We analysed the two groups with the Mann-Whitney U test for the non-normally distributed variables. Logistic regression analysis was performed to explore the variables independently associated with the presence of RLS. P<0.05 was considered significant.

Results

The study included 201 patients [152 females (75.6%), 49 males (24.4%), with the mean age of 34.6 years±11.6] diagnosed with migraine with or without aura, and 102 headache-free participants [67 females (65.7%), 35 males) (34.3%), mean age 31.9 years±10.8] were included. There was no statistically significant difference between the two groups in terms of age and gender.

More patients (40.3%, n=81) in the migraine patients met the diagnostic criteria for RLS than the headache-free group (15.7%, n=16) (p<0.001).

The number of patients with RLS was 81 (40.3%) and those without RLS was 120 (59.7%). 77.8% of RLS (+) and 74.2% of RLS (-) migraine patients were female (p=0.559). The two groups were similar in terms of age, number of attacks per month, presence of aura, smoking, and family history for RLS. Length of disease was longer in the (+) migraine patients with RLS than RLS (-) group (mean 14.6±9.7 years and 4.6±5.0 years respectively, p<0.001). Five of six patients with both hypertension and migraine patients had RLS (76 of 195 for patients without hypertension, p=0.041) (Table 1). Serum ferritin levels were below 50 mL/ng in 74.2% of RLS (+) migraine patients and 79% of RLS (-) migraine patients and there was

no statistically significant difference (p=0.526). Serum Hb levels of the two groups were within normal laboratory values (83.3%, 90.1% of patients, respectively, p=0.173). Additionally, the migraine patients with severe/very severe RLS (n=20) had a longer disease duration than the patients with mild/moderate RLS (n=61) (18.3±9.7 years, 13.4±9.5 years; p=0.050).

Logistic regression analysis showed a significant association the disease duration and the presence of RLS (Odds ratio: 13.25, 95% confidence interval: 5.62-31.24), p=0.001). Other potential covariates age, gender, aura, the frequency of attacks, length of disease, family history, hypertention, smoking status, Hb and ferritin level showed no significant association with the presence of RLS in migraineurs (Table 2).

Discussion

This study showed that RLS was more common in patients with migraine than headache-free volunteers (40.3%/15.7%). Moreover, RLS was more frequent in migraine patients with hypertension, the frequency and severity of RLS was related to the disease duration.

The frequency of RLS in healthy populations has been reported to be approximately 10% (15). However, studies also showed that this rate is approximately two to three times higher in patients with migraine. First, headache and RLS comorbidity was reported by Young et al. (16) with higher prevalence of RLS in 50 patients with headache. Later, in a case-controlled study matched for age and gender, among 411 migraine patients the frequency of RLS was significantly higher compared with the controls (17.3%/5.6%) (17). In a population-based study from Taiwan, 23.641 migraine patients and 94.564 people without migraine were compared, and an increased risk of RLS was found in migraineurs regardless of the comorbidities and migraine type (18). The prevalence of RLS in migraine patients was 33% in a single case-control study from Turkey (12). Our observation of 40.3% RLS among migraine patients is in agreement with that study. Also consistent with the literature, we found that the presence of RLS in migraineurs was about three times higher than in headache-free controls (17).

Several hypotheses have been proposed regarding the higher prevalence of RLS in migraineurs The most important of these is the idea that dopamine and iron regulation disorders are mechanisms that can lead to both conditions (19,20). The reasons suggesting that the dopaminergic system affects the pathophysiology of both RLS and migraine are as

Table 1. Demographic and clinical characteristics of migraine patients with and without RLS

	RLS (+) (n=81)	RLS (-) (n=120)	p value
Age (year), mean±SD	36.1±12.5	33.5±10.9	0.128*
Female, n (%)	63 (77.8)	89 (74.2)	0.559**
Length of disease (year), mean±SD	14.6±9.7	4.6±5.0	0.001*
Presence of aura, n (%)	9 (11.1)	14 (11.7)	0.903**
Smoking, n (%)	26 (32.1)	28 (23.3)	0.281**
Hypertension, n (%)	5 (6.2)	1 (0.8)	0.040**
Frequency of attacks			0.442**
Episodic, n (%)	76 (93.8)	109 (90.8)	-
Chronic, n (%)	5 (6.2)	11 (9.2)	-

*The independent samples t-test was used for analyses.
**The chi-square test was used for analyses.
SD: Standart deviation, RLS: Restless legs syndrome

Table 2. Regression coefficients of logistic regression of migraine patients with RLS

	OR	95% CI	p value
Age	1.02	0.99-1.04	0.11
Gender	0.89	0.38-2.06	0.79
Presence of aura	0.74	0.28-1.95	0.55
Length of disease	6.19	3.40-11.26	0.000
Headache frequency	0.75	0.42-1.32	0.32
Family history	1.75	0.46-6.58	0.40
Hypertension	7.89	0.89-68.31	0.06
Hb level	1.99	0.78-5.03	0.51
Ferritin level	0.70	0.30-1.58	0.39
Smoking status	1.51	0.77-2.98	0.22

OR: Odds ratio, CI: Confidence interval, RLS: Restless legs syndrome, Hb: Hemoglobin

follows: Dopamine-mediated symptoms (like yawning and gastrointestinal symptoms) before migraine attacks, dopamine agonists increase migraine symptoms, animal studies showed that dopaminergic pathways are involved in both RLS and migraine, and dopamine agonists are effective for treating RLS (21-23).

Concerning the iron metabolism hypothesis; it has been reported that iron deposits are observed in the deep brain nuclei in patients with migraine and that recurrent migraine attacks are related to these iron stores (24). Iron deficiency affects RLS etiology (25). Based on this information, it is thought that iron storage and therefore usable iron deficiency may be one of the common pathophysiological mechanisms of these two diseases. Besides, since iron is the cofactor of tyrosine hydroxylase, a enzyme required in the synthesis of dopamine, it may be that striatal dopamine neurotransmission is impaired in brain iron metabolism disorders and this situation leads to RLS (26). Unlike previous studies that indicated a common mechanism regarding iron metabolism, serum Hb and ferritin levels were similar in migraine patients with and without RLS in our study.

Various studies have reported the presence of RLS in migraine sufferers was related to the characteristics of the patient and disease (11). Age, family history for RLS, length of disease, comorbidities, frequency, and severity of headache can predict RLS occurrence (17,18,27,28).

It has been concluded in some studies that migraineurs with a longer disease duration are more likely to have RLS (12,18,27). Similar to the previous studies, long migraine duration was associated with increased frequency of RLS in our study, some authors consider that this association occurs due to central sensitization. In central sensitization, due to the plasticity of the somatosensory nervous system in response to chronic pain, the activity of neurons and nociceptive pathways increases and this causes pain, allodynia or hypersensitivity (29). This may also be one reason why the severity of RLS, which is another significant finding, increases as the duration of the disease increases (30).

Hypertension was significantly higher in migraine patients with RLS in our study. Previous studies also showed that hypertension is more common in patients with RLS (31). It was suggested that the presence of periodic leg movements during polysomnography increases blood pressure transiently (32). Additionally, in a study-separated patients as primary and secondary RLS, patients with primary RLS were younger and the prevalence of hypertension did not increase, whereas the rate of hypertension diagnosis was more common in patients with secondary RLS (33).

This study has some limitations. Since it was conducted a cross-sectional study the temporal relationship between the diagnosis of migraine and the presence of RLS symptoms could not be evaluated. Whether the symptoms are improved after migraine treatment was also not evaluated. The number of participants in both the patient and headache-free groups were also low.

Conclusion

In conclusion, we observed a higher frequency of RLS in patients with migraine than controls. We also observed a positive association between the frequency and severity of RLS and the duration of migraine. Since both diseases negatively affect the quality of life, RLS symptoms should be screened especially when migraine is diagnosed.

Ethics

Ethics Committee Approval: The study were approved by the Erciyes University Clinical Research Local Ethics Committee (decision no: 2021/147, date: 03.03.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç.S., B.S.A.P., N.K., Concept: M.C.A., Design: B.S.A.P., M.C.A., Data Collection or Processing: A.Ç.S., B.S.A.P., N.K., Analysis or Interpretation: A.Ç.S., B.S.A.P., M.C.A., Literature Search: A.Ç.S., B.S.A.P., N.K., Writing: A.Ç.S., B.S.A.P., M.C.A.

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