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ORIGINAL ARTICLE

Relationship between primary restless legs syndrome and migraine with aura

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Abstract In this study, the prevalence and characteristics of definite migraine in primary restless legs syndrome (pRLS) patients and matched control patients (CPs) were investigated. We evaluated 63 consecutive adult pRLS patients and 141 age- and sex-matched controls in this case–control study. The diagnosis of migraine and its subtypes were defined based on *The International Classification of Headache Disorders-II*. Only those with "definite" migraine were included in the study. The mean age of 63 adult pRLS patients (15 men and 48 women) who participated in the study was 49.4 years. A total of 27 patients (42.9%) had definite migraine. Of these migraineurs, seven (11.1%) were without aura and 20 (31.8%) were with aura. The mean age of the 141 matched CPs was 48.7 years. A total of 32 CPs (22.7%) experienced migraine. Among these 32 migraineurs, 28 (19.9%) were without aura and four (2.8%) were with aura. Migraine and migraine with aura were significantly more common in pRLS patients than in CPs. pRLS patients with migraine were more anxious and experienced a shorter duration of RLS symptoms than pRLS patients without migraine. Migraineurs in the pRLS group tended to have high scores for severity of migraine headache by Visual Analog Scale score and high levels of disability by Migraine Disability Assessment

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grading than those in the control group. pRLS patients showed a positive association with definite migraine headaches. In contrast to results highlighted in recent studies, we found a strong link between migraine with aura and pRLS.

Introduction

Restless legs syndrome (RLS) is a prevalent sensory motor disturbance characterized by distressing deep sensations in the limbs, particularly the legs, associated with an urge to move, often during rest [1]. RLS affects approximately 4—29% of the general population, predominantly females (female-to-male ratio 2:1) [2]. In most cases, the etiopathogenesis of RLS is idiopathic, although some secondary etiologies such as iron deficiency, pregnancy, uremia, diabetes mellitus, polyneuropathy, rheumatoid arthritis, and spinal disorders may be present [3]. However, its pathophysiology remains unclear to date.

Migraine is a common primary headache disorder that affects approximately 10—20% of the general population, especially females (female-to-male ratio of 2—3:1) [2]. It has been reported that migraine may be complicated by a number of comorbidities, such as stroke, cardiovascular disease, anxiety and depressive disorders, epilepsy, irritable bowel syndrome, and pain disorders [2,4].

The similar prevalence, female-to-male ratio, pathophysiology (unclear in both), and complications and comorbidities of migraine and RLS have attracted increasing attention in clinical practice. An association between primary headaches, especially those of migraine and RLS in adult patients, has been reported. The prevalence of migraine was reported to be higher in pRLS patients than in general population [3,5]. It has also been confirmed that RLS is more common in patients with migraine than in those without migraine [6—10].

In the current study, our main objective was to compare the prevalence of subtypes of definite migraine (with or without aura) in primary RLS (pRLS) patients and matched control patients (CPs) to study the association between both diseases. The secondary objective was to determine whether or not family history, severity of diseases, the presence of anxiety and depressive disorders, or sleep quality exhibited any differences between pRLS patients and CPs. We also determined whether there were any differences in the severity of sleep disturbances, migraine headache, and anxiety or depression between migraineurs in the pRLS group and those in the control group.

Methods

Sample of patients and CPs

In this study, 340 consecutive patients (age >18 years) suffering from RLS symptoms followed at the outpatient clinic of the Department of Neurology at the Sakarya University (Sakarya, Turkey) between July 2014 and November 2015 were informed about the study.

Only patients with pRLS diagnosed according to the standard diagnostic criteria of International Restless Legs Syndrome Study Group (IRLSSG) [11] were examined in detail. Two patients declined participation; 170 patients with RLS symptoms did not participate in further investigations for eliminating the secondary causes of RLS. Secondary causes of RLS were detected in 40 patients (1 with chronic back pain after lumbar spinal instrumentation surgery; 1 with active patellofemoral osteoarthritis with elevated C-reactive protein level, erythrocyte sedimentation rate, and white blood cell count; 3 with venous insufficiency with ultrasonographic evidence; 8 with diabetes mellitus, which was clinically, laboratory, and/or electrophysiologically proven; and all others diagnosed with iron deficiency with or without anemia) and they were all excluded from the study.

We also excluded patients using any medication or receiving medical treatment or diagnosed with "probable" migraine or with "definite" migraine in addition to any other primary headaches. Only 63 pRLS patients (15 men and 48 women) with a mean age of 49.4 ± 11.7 years (22—85 years) who fulfilled all study criteria were thus eligible to participate in this study. Figure 1 shows the recruitment of patients to the pRLS group.

Age- and sex-matched CPs were selected. The physical and neurological examination results of all CPs were normal, and they did not have any clinical evidence of RLS and/or systemic disorders. Patients in the control group also went through the same laboratory and clinical assessments as the patients in the pRLS group. Patients were excluded according to the criteria specified for the pRLS group. Of the 240 CPs informed about the study, 141 CPs (44 men and 97 women) with a mean age of 48.7 ± 8.1 years (27—61 years) were eligible and included in the study. Figure 2 shows the recruitment of patients to the control group.

The Ethical Committee of Sakarya University School of Medicine provided ethical approval for this study. Informed written consent was obtained from each patient included in this study.

Data collection

Sociodemographic data, including age, sex, medical history of the patient, and his/her family medical history, were collected. Patients were asked about similar symptoms for RLS and migraine in their close relatives. Family history was considered positive if any first-degree relative was reported

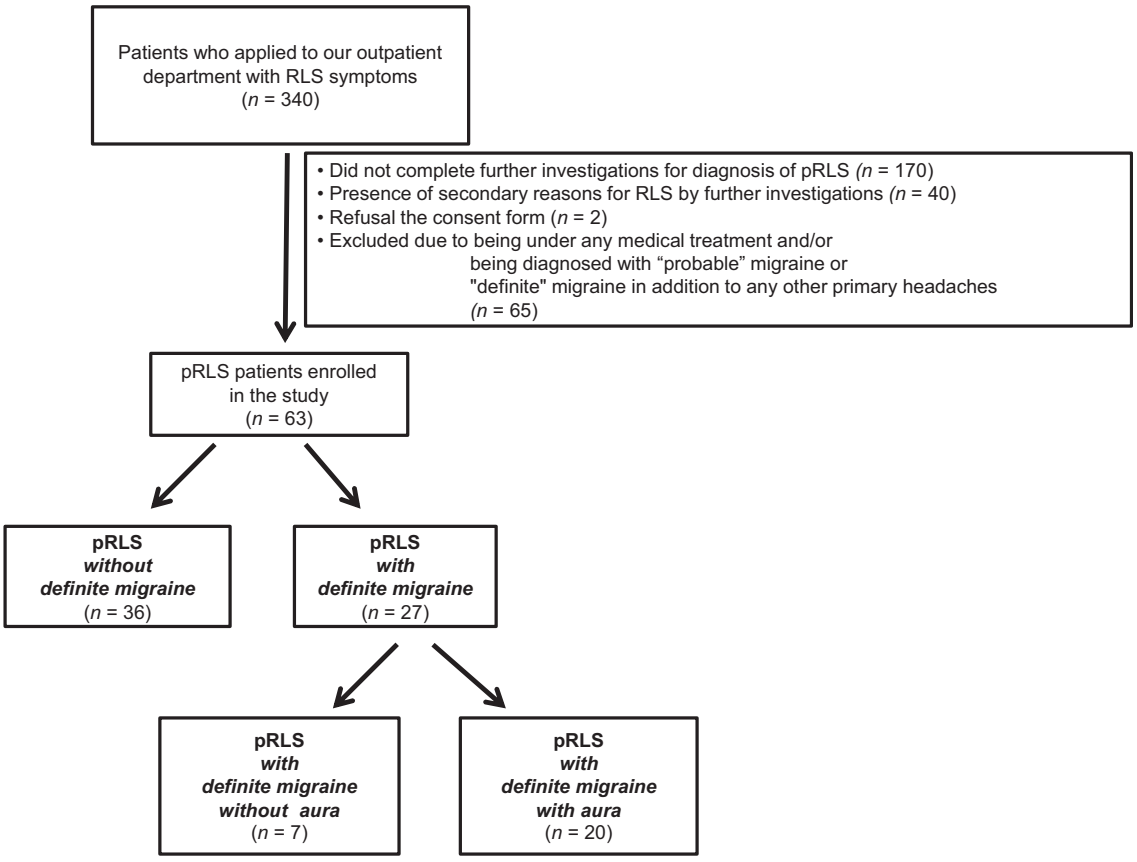

Figure 1. Flowchart showing recruitment of patients to the primary restless legs syndrome (pRLS) group.

to have had such symptoms. Information about the presence of the following comorbid conditions was obtained from all study patients: anemia, diabetes mellitus, kidney disease, neuropathy, peripheral vascular diseases, osteoarthritis, rheumatologic diseases, thyroid disorders, or other nondefined conditions. Women of reproductive age were questioned about their known pregnancy status or any recent menstrual cycle disorder. To evaluate conditions that may cause symptomatic RLS, the following laboratory data were collected: serum hemoglobin, serum urea, serum creatinine, serum iron, total iron-binding capacity, serum ferritin, erythrocyte sedimentation rate, C-reactive protein, hemoglobin A1c test and fasting blood glucose, and thyroid function test results. Patients with any secondary causes of RLS, either self-reported in their medical history or by abnormalities identified in laboratory tests, were excluded from the study.

Clinical examinations

Neurologists and internists performed thorough neurological examinations and electromyography and physical assessments for differential diagnosis of RLS and for exploring any comorbidity in the study patients. A hematologist assessed specific laboratory data. Standard Doppler ultrasound examinations were performed by a radiologist to investigate disturbances in the lower extremities venous system for all patients with RLS symptoms.

Assessment of RLS

Patients with pRLS were investigated by RLS diagnostic interview using the 2012 Revised IRLSSG diagnostic criteria for RLS and supported as a case of idiopathic RLS by physical, neurological, electrophysiological, and radiological examinations and laboratory data [11,12].

Assessment of migraine

Neurologists assessed the patients and classified their migraine subtypes according to the International Classification of Headache Disorders-II [13]. Only patients diagnosed with "definite" migraine were considered to be suffering from migraine and included in the study as migraineurs. The "migraine with aura" subtype was selected if over 90% of the migraine attacks of the patients were with aura, as assessed by self-reporting. All patients with a diagnosis of "probable migraine" and/or "other types of primary headaches" were excluded from the study.

Questionnaires

All study participants completed a battery of validated questionnaires, including the IRLSSG Severity Scale (IRLSSS) [13], Migraine Disability Assessment (MIDAS) [14], Visual Analog Scale (VAS) [15], Beck Anxiety Inventory (Beck-A)

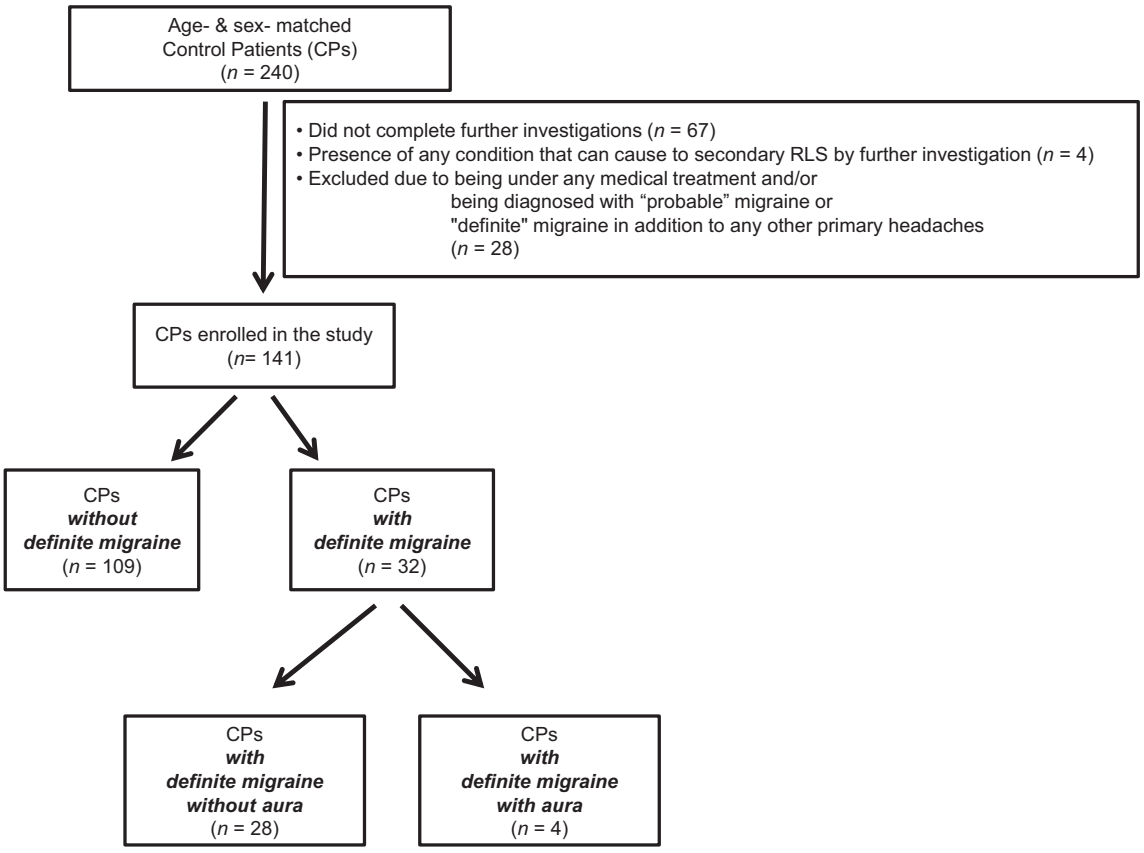

Figure 2. Flowchart showing recruitment of patients to the control group. CPs = control patients.

[16], Beck Depression Inventory (Beck-D) [17], and Pittsburgh Sleep Quality Index (PSQI) [18].

Statistical analyses

SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. Kolmogorov–Smirnov test was used as the normality test. Differences between continuous data that were distributed normally were evaluated using a Student *t* test. Differences between the two groups were evaluated using a Chi-square test. Pearson correlation was used to evaluate the correlation of Beck-D, Beck-A, MIDAS, and VAS scores. Statistical significance was set at $p < 0.05$.

Results

In this case–control study, the mean age of 63 adult pRLS patients (15 men and 48 women) was 49.4 ± 11.7 years, and the mean age of 141 CPs (44 men and 97 women) was 48.7 ± 8.1 years. We did not detect any differences between the two groups in terms of age and sex. Patients with pRLS were found to have significantly more frequent positive family history of RLS and migraine, compared with CPs. Significantly higher depression, anxiety scores, and a worse sleep quality average were observed in pRLS patients in comparison with CPs. Among the 63 pRLS patients, 27 (42.9%) had migraine. Of these migraineurs, 20 (31.7%) had migraine with aura and seven (11.1%) had migraine without aura. Among the 141 CPs, 32 (22.7%) experienced migraine; among these 32 migraineurs, four (2.9%) had migraine with aura and 28 (19.9%) had migraine without aura. Migraine and migraine with aura were significantly more common in pRLS patients than in CPs. Demographic and clinical features and the prevalence of migraine in the study sample are presented in Table 1.

To clarify the impact of migraine on the variables in pRLS patients, we compared different variables between pRLS patients with migraine and pRLS patients without migraine. There were no statistical differences in RLS severity and sleep quality between these two groups. The duration of RLS (measured in years) was greater in pRLS patients without migraine, whereas pRLS patients with migraine were more anxious. Although not statistically significant, depression occurred more frequently in pRLS patients with migraine. Details of the impact of definite migraine on the variables in pRLS patients are given in Table 2.

Duration of migraine in migraineurs in the pRLS group was higher than in those in the control group. Compared with migraineurs in the control group, migraineurs in the pRLS group had high scores for severity of migraine headache, as indicated by the VAS score ($p = 0.041$), and high levels of disability, as indicated by the MIDAS grading ($p = 0.001$). Details of the severity of migraine in the population studied are presented in Table 3.

MIDAS grading in migraineurs was positively correlated with PSQI ($r = 0.405$, $p < 0.0001$), Beck-D ($r = 0.474$, $p < 0.0001$), and Beck-A ($r = 0.258$, $p < 0.001$) scores. In addition, the VAS score of migraineurs showed positive correlations with PSQI ($r = 0.306$, $p = 0.026$), Beck-A

Table 1 Demographic and clinical features and the prevalence of migraine in the study sample.

	Control group (n = 141)		pRLS group (n = 63)		p
	n	%	n	%	
Sex					
Male	44	31.2	15	23.8	0.28
Female	97	68.8	48	76.2	
Age (y)	48.7 ± 8.1		49.4 ± 11.7		0.62
Beck-D score	8.4 ± 6.8		16.0 ± 9.1		<0.0001
Beck-A score	11.9 ± 11.5		21.6 ± 12.9		<0.0001
PSQI score	5.2 ± 3.1		10.9 ± 3.9		<0.0001
Family history of RLS	0	0	36	57	<0.0001
Family history of migraine	12	8.5	19	30.2	<0.0001
Migraine (+)	32	22.7	27	42.9	<0.0001
Migraine with aura	4	2.8	20	31.8	<0.0001
Migraine without aura	28	19.9	7	11.1	<0.0001

Beck-A = Beck Anxiety Inventory; Beck-D = Beck Depression Inventory; pRLS = primary restless legs syndrome; PSQI = Pittsburgh Sleep Quality Index.
Age, Beck-D, Beck-A, and PSQI scores are presented as the mean ± SD. All other variables are presented as number.

Table 2 Demographic and clinical features of the pRLS patients with or without migraine.

Variable	pRLS without migraine (n = 36)	pRLS with migraine (n = 27)	p
RLS duration[a]	14.9 ± 10.6	8.9 ± 7.7	0.01
IRLSSS score	25.7 ± 6.7	25.3 ± 7.2	0.79
Beck-D score	13.8 ± 8.9	18.3 ± 8.9	0.05
Beck-A score	18.0 ± 11.9	26.7 ± 12.8	0.008
PSQI score	10.6 ± 4.1	11.1 ± 3.7	0.64

Beck-A = Beck Anxiety Inventory; Beck-D = Beck Depression Inventory; IRLSSS = International Restless Legs Syndrome Study Group Severity Scale; pRLS = primary restless legs syndrome; PSQI = Pittsburgh Sleep Quality Index.
All variables are presented as the mean ± SD.
[a] Duration of symptoms of RLS by history in years.

Table 3 Migraine duration, MIDAS grades, and VAS scores of patients with migraine.

	Control patients with migraine (n = 32)	pRLS patients with migraine (n = 27)	p
Migraine duration[a]	6.7 ± 4.9	8.9 ± 6.7	0.918
MIDAS score (point)	0.35 ± 0.06	0.80 ± 0.15	0.001
MIDAS Grade I (n)	24	10	
MIDAS Grade II (n)	7	12	0.001
MIDAS Grade III (n)	1	4	
MIDAS Grade IV (n)	0	1	
VAS score (point)	5.9 ± 1.6	7.0 ± 2.0	0.041
VAS score 0 (n)	4	2	
VAS score 1–4 (n)	4	2	
VAS score 5–6 (n)	16	5	0.001
VAS score 7–10 (n)	8	18	

MIDAS = Migraine Disability Assessment; pRLS = primary restless legs syndrome; VAS = Visual Analog Scale.
Migraine duration, MIDAS score (point), VAS score (point) are presented as the mean ± SD. All other variables are presented as number.
[a] Duration of migraine by history in years.

(r = 0.281, p = 0.042), and migraine duration (r = 0.615, p < 0.0001). Details of these correlations are presented in Table 4.

Discussion

The primary desired outcome of this study was to evaluate whether there is a relationship between definite migraine and pRLS, and our findings do confirm an association. We detected a higher frequency of definite migraine in pRLS patients than in CPs and the presence of aura in migraineurs influenced this relationship. Gupta et al. [19] reported that migraine is frequently comorbid (44.4%) with idiopathic RLS. This ratio is very close to that found in this study (42.9%). d'Onofrio et al. [20] demonstrated that the association between migraine and RLS is specific for the

Table 4 Correlations between MIDAS, IRLSSS, VAS, migraine duration, Beck-A, Beck-D, and PSQI.

	PSQI	Beck-D	Beck-A	Migraine duration[a]	VAS	IRLSSS	MIDAS
MIDAS	0.405*	0.474*	0.258*	0.082	0.330**	0.176	
IRLSSS	0.448*	0.091	0.099	0.272	0.365		
VAS	0.306**	0.116	0.281**	0.615**			
Migraine duration[a]	0.358*	0.150	0.355*				
Beck-A	0.515*	0.723*					
Beck-D	0.605*						
PSQI							

Beck-A = Beck Anxiety Inventory; Beck-D = Beck Depression Inventory; IRLSSS = International Restless Legs Syndrome Study Group Severity Scale; MIDAS = Migraine Disability Assessment; PSQI = Pittsburgh Sleep Quality Index; VAS = Visual Analog Scale.
*Correlation is significant at the 0.01 level (two tailed).
**Correlation is significant at the 0.05 level (two tailed).
[a] Duration of migraine by history in years.

"migraine without aura" subtype. Fernández-Matarrubia et al. [5] also found a potential relationship between RLS and migraine, in particular for the migraine without aura subtype, as opposed to our findings.

The pathophysiology of RLS is still unclear but peripheral and central mechanisms within the nervous system have been suggested to play a role. Besides the coincidental presence of migraine, especially migraine with aura and pRLS, three mechanisms may be considered for this comorbidity. The first mechanism can be attributed to the role of iron. An association between iron and RLS was noted previously and iron insufficiency was found to be the strongest environmental risk factor associated with RLS [21]. It was also shown that RLS severity is correlated with peripheral iron insufficiency. In addition, conditions that compromise iron status such as anemia, pregnancy, and end-stage renal disease have been associated with an increased risk of RLS [22]. However, so far, the pathogenesis of migraine attacks with aura remains unclear. Brain iron deposition in multiple deep nuclei is involved in migraine attack pathogenesis, while low brain iron levels in RLS patients have also been demonstrated [23—25]. In our study, none of the patients were anemic and all had normal serum levels of iron and ferritin. Nevertheless, this does not necessarily reflect the central nervous system iron status. This complex mechanism of regional iron dysregulation in both pRLS and migraine with aura patients calls for further investigation. The second possibly related mechanism is concerning the role of dopamine. Pharmacological treatment data and some imaging data strongly support a dopaminergic abnormality in RLS cases [26,27]. Use of dopaminergic drugs may trigger episodes of migraine, whereas dopamine antagonists can have an antimigraine effect [28]. Considering the impact of dopaminergic or other drugs while not underestimating their impacts, in this study, we excluded all patients using any medications (antimigraine drugs, dopamine agonists, sleep medicines, antidepressants, antihistamines, etc.). Third, the role of spreading depression (SD) model may be another common mechanism. Previously, migraine with aura has been only considered as a vascular process after vasoconstriction (i.e., as an initial event when head pain occurs due to reactive vasodilatation) [24,29,30,31]. This concept refers to the SD hypothesis, which suggested that there is a spreading reduction in cerebral blood flow or spreading oligemia in migraine with aura patients. Such an approach triggered a revolution in thinking about migraine—aura [32]. A profound depolarization of neurons and propagation of glial cells in a wave-like manner across these brain regions may can be considered as a common pathophysiology for both migraine—aura and RLS. In fact, in RLS patients, as well as in those with migraine and aura, the SD model plays a role. This is particularly relevant as dopamine levels are reduced in several areas of the central nervous system, including the striatum and midbrain (dopaminergic cell group), which are two important regions for RLS circuitry [31,33]. Further investigations should therefore be conducted for RLS and SD.

The second outcome of this study was to determine whether any relationship between family history of migraine and family history of RLS was significantly more frequent in pRLS patients than in CPs. In idiopathic RLS patients, the frequency of family history of RLS is expected to be high. However, the high frequency of family history of migraine together with family history of RLS led us to assume a common genetic pathophysiology. As a result, we divided the pRLS patients into two groups: pRLS patients with migraine and pRLS patients without migraine. In our analysis between these two groups, the duration of RLS (years) was found to be longer in pRLS patients without migraine, as can be seen in Table 2. Thus, we feel that there must be some desensitization mechanisms that intercept migraine headaches in pRLS patients in terms of disease duration. Besides, pRLS patients with migraine were more anxious than pRLS patients without migraine. However, depression was not as significant as anxiety in these patients. Depression, anxiety, and migraine may be causally related or perhaps share a common genetic and/or environmental pathophysiology. They may also be different phenotypic expressions of the same disorder [34].

The third outcome of this study was that pRLS patients were more anxious, more depressive, and had worse sleep quality than CPs. Having a definite migraine headache did not increase the severity of pRLS in IRLSSS (Table 2). However, migraine is more severe and more disabling for migraineurs in the pRLS group than for those in the control group (Table 3). Therefore, the impact of pRLS on migraine seems to be greater than the impact of migraine on pRLS. In addition, the correlations between VAS scores and PSQI, Beck-A, as well as the correlations between MIDAS grading and PSQI, Beck-D, and Beck-A scores were remarkable. Improvements in sleep disturbances, anxiety,

and depression in pRLS patients with migraine may be possible if these are treated along with migraine. More studies should be planned to investigate such outcomes.

Limitations

A major limitation of our study was the relatively small sample size.

Conclusion

Adult pRLS patients showed positive associations with definite migraine headaches. In contrast to other recent studies, we found a strong link between migraine with aura and pRLS. This information may provide a better understanding of the comorbidity and pathophysiology of pRLS and migraine with aura.

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