Restless Leg Syndrome in Hospitalized Psychiatric Patients in Mashhad

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Background and Objective   Sleep disorders, especially restless leg syndrome (RLS), have in recent years been recognized as common problems that increase the risk of mental disorders, anxiety, and depression, and lead to decreased quality of life and social isolation. The aim of this cross-sectional study was to evaluate the frequency of RSL in psychiatric patients admitted to Ibn Sina Hospital, Mashhad, Iran during 2020−2021.

Methods   Eligible individuals were selected using available sampling, and after determining the type of psychiatric disorder, the demographic and medical information of patients were recorded. The RLS assessment questionnaire was used to evaluate the purpose of the study.

Results   Of the 150 hospitalized patients with psychiatric disorders, 67 (44.7%) were male, and the mean age of the subjects was 34.63 ± 10.80 years. RLS was not observed in 100 patients (66.7%); however, mild RLS was shown in 33 patients (22%), while severe type was shown in 17 patients (11.3%). The prevalence of major depressive disorder and lithium consumption was significantly higher in people with RLS than in those without the syndrome ($p = 0.047$ and $p = 0.012$, respectively).

Conclusions   These results indicate that there is a relationship between the prevalence of RLS and some psychological disorders and medications that are commonly used in this field. Managing the symptoms of this syndrome by better understanding its predisposing factors can lead to better management of patients.   **Sleep Med Res 2023;14(3):161-167**

Keywords   Restless legs syndrome; Psychiatric disorders; Ibn Sina Hospital; Mashhad.

INTRODUCTION

In recent years, sleep disorders have been considered a new emerging field in medicine, and their roles in some unrelated clinical problems have been confirmed [1]. Indeed, sleep hygiene plays an important role in the concentration and quality of life [2]. Sleep is defined as a transient reduction in the level of consciousness, but nevertheless the body is physiologically active, and all kinds of dynamic fluctuations in the central nervous system and hemodynamic changes occur in the respiratory and metabolic systems [1]. Over the past decades, the prevalence of sleep disorders has increased because of the stressful and competitive conditions of modern societies [3].

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

(DSM-5) scale, sleep disorders can be classified as insomnia, hyper somnolence, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, non-REM sleep arousal disorders, nightmare disorder, REM sleep behavior disorder, restless leg syndrome (RLS), and substance/medication induced sleep disorder [4].

In patients who complain of a feeling of being forced to move their legs while lying in bed or while sitting, RLS should be considered, especially if the symptoms are more severe at night. There is no specific test for RLS, so the condition is diagnosed by a physician evaluation. The five basic criteria for clinically diagnosing RLS include having a strong, often irresistible urge to move the legs, usually accompanied by uncomfortable sensations, worsening symptoms in sitting or lying down positions, relieving symptoms by activities such as walking or stretching, worsening symptoms at night, and symptoms that cannot be explained solely by another medical or behavioral condition [5,6].

Several studies have confirmed some risk factors for RLS, which include being female [7], increasing age, parkinsonism, peripheral neuropathy, subjective cognitive impairment, acting out dreams, hyposmia, active smoking and cardio metabolic diseases [5,7,8], and medication [9].

According to Ohayon [5] and Tison et al. [7], the prevalence of RLS in the general population was 6% and 8.5%, respectively. Agüera-Ortiz et al. [6] found that 11.11% of 100 non-demented psycho-geriatric outpatients in their study were diagnosed with RLS. Leutgeb and Martus [9] studied 243 individuals with mood and anxiety disorders who were interviewed for symptoms of RLS, and they found the overall prevalence of RLS to be 27%. Allen et al. [10] discovered that out of 15391 participants, 1114 individuals (7.2%) reported RLS symptoms, with 416 (2.7%) experiencing symptoms at least 2 times per week and finding them moderately or severely distressing. In 2000, Rothdach et al. [11] found the overall prevalence of RLS to be 9.8%, which was higher in women (13.9%) than in men (6.1%).

Lee et al. [12] examined the association between RLS and DSM-IV major depressive disorder and panic disorder and found that the adjusted odds ratio for the diagnosis of major depressive disorder (4.7%), panic disorder (12.9%), and comorbidity of major depressive disorder and panic disorder (9.7%) in the past 12 months suggested a strong association between RLS and major depressive disorder and/or panic disorder.

While RLS prevalence in the community population has been studied, the prevalence of RSL in the psychiatric population in Iran has never been investigated. The aim of the present study is to evaluate the frequency of RLS in psychiatric patients who were admitted to Ibn Sina Psychiatric Hospital in Mashhad.

METHODS

The present prospective, cross-sectional, and descriptive-analytical study was carried out between 2021 and 2022 to evaluate the prevalence of RLS among patients hospitalized in Ibn Sina Hospital in Mashhad, Iran. For this purpose, an RLS diagnosis questionnaire was designed. The questionnaire was composed of four questions based on a Likert 4-point scale (never, sometimes, most of the time, always), where each question was scored from 0 to 3, the total score being 0 to 12. The scores ranging 0−4, 4−7, and 8−12 were assigned to without RLS, mild RLS, and severe RLS, respectively. The reliability of the Persian version of the RLS questionnaire was obtained by calculating the Cronbach's alpha of 0.97 in similar studies in Iran [13]. In addition, the patient's epidemiologic data, history of medications, and any psychiatric disorder were recorded.

All of the patients who were between 18 and 60 years old and had met the inclusion criteria were selected for the rest of the study. The inclusion criteria included: age 18−60 years old, history of hospitalization in a psychiatric hospital during a 1-year research period, lack of cognitive impairment, and lack of pervasive developmental disorders and intellectual disability that would prevent cooperation in completing the questionnaire and completing and signing of the informed consent form. On the other hand, patients in the withdrawal or intoxication phase of a substance use problem, or with confirmed pregnancy (according to preadmission examination), or who were admitted solely for addiction treatment and did not have another concomitant psychiatric disorder, or who showed lack of cooperation in conducting the research, were excluded from the rest of the study.

In the next step, the demographic data and medical record of patients were obtained, and the type of psychiatric disorder was diagnosed according to the DSM-5 criteria. Prescribed psychiatric drugs (for better discrimination between RLS and akathisia symptoms), history of drug abuse (alcohol, nicotine, caffeine, and other substances), working a night shift, or having suicidal thoughts, were evaluated and recorded in the patient medical file. Serum level of hemoglobin (Hb), urea, and creatinine were obtained from preadmission examination data. Cases with obvious anemia or uremia were considered as confounding factors and excluded from the rest of study. RLS diagnosis and differentiation from other disorders, like akathisia and arthritis, were determined via clinical interview and completion of the RLS assessment questionnaire.

Ethics Statement

This study was approved by the Ethics Committee of Ibn Sina Hospital (IR.MUMS.MEDICAL.REC.1397.770). Before the starting the study, the informed consent document was obtained from all participants.

Statistical Analysis

For statistical analysis of the data, SPSS software (Ver. 22; IBM Corp., Armonk, NY, USA) was used. The mean ± standard deviation was used for quantitative data with normal distribution.

Independent t-test and Mann−Whitney test were used for the intergroup comparison of qualitative data. To investigate the variables affecting the RLS event, the backward logistic regression model was used. Significance level of 0.05 was considered.

RESULTS

In this study, 150 hospitalized patients completed the survey. The participants were 34.63 ± 10.86 years old. Of these, 83 (55.3%) were female; the RLS questionnaire score indicated no sign in 100 (66.7%), mild in 33 (22%), and severe RLS sign in 17 (11.3%) individuals. In terms of underlying disease, 32 (21.33%) participants were diagnosed with bipolar 1 disorder, 8 (5.33%) with major depressive disorder, and 4 (2.66%) with schizophrenia. In relation to the medications used, 78 (52%) participants were taking valproate sodium, 70 (46.7%) were taking lorazepam, 46 (30.7%) were taking lithium, and 36 (24%) were taking quetiapine. Also, 20 (13.33%) participants had suicidal ideas, 19 (12.66%) participants were using nicotine, while 4 (2.66%) participants worked night shift (Table 1).

Age, gender, red blood cell (RBC) count, level of Hb, urea, creatinine, night shift history, suicidal thoughts, and substance abuse showed no significant difference between participants with and without RLS (Table 1).

There was a significant difference between taking lithium and the presence of RLS (p = 0.012). However, there was no significant difference between taking other drugs and the presence of RLS (Table 2).

Comparison of patients with and without RLS in terms of various psychiatric disorders showed that the prevalence of major depressive disorder in individuals with RLS was significantly higher than in patients without RLS (p = 0.047) (Table 3). On the other hand, the prevalence of schizophrenia in the group without RLS was significantly higher than in individuals with RLS (p = 0.044). There was no significant difference between other disorders in patients with RLS (Table 3).

To investigate the variables affecting the RLS event, age and sex variables along with significant variables (at a significance level of 0.1) were included in the backward logistic regression model. Two variables of lithium and clonazepam prescription were identified as effective variables. Table 4 shows that taking lithium increases the chance of developing RLS by 2.8 times, while taking clonazepam reduces the chance of developing this syndrome. Other significant variables, such as major depressive disorder and schizophrenia, did not have a significant effect on the incidence of RLS (Table 4).

DISCUSSION

This study revealed an RLS prevalence of 33.3% in the psy-

chiatric patients hospitalized in Ibn Sina psychiatric hospital in Mashhad, Iran. In comparison of patient with and without RLS, there was no significant difference observed in terms of gender, medical history, night shift work, suicidal ideation, substance

Table 1. Comparison of epidemiologic factors and laboratory findings in patients with and without RLS

Characteristic	RLS		p-value
	Yes (n = 50)	No (n = 100)	
Age (yr)*	34.68 ± 11.84	34.60 ± 10.40	0.967
Gender			0.417
Male	20 (40)	47 (47)	
Female	30 (60)	53 (53)	
Medical history			
Hypothyroidism	1 (12.5)	6 (33.3)	-
High blood pressure	3 (37.5)	1 (5.6)	
Diabetes	2 (25)	5 (27.8)	
Seizures	2 (25)	6 (33.3)	
Nightshift working			0.466
Yes	4 (8)	5 (5)	
No	46 (92)	95 (95)	
Suicidal thoughts			0.137
Yes	20 (40)	28 (28)	
No	30 (60)	72 (72)	
Drug abuse			
Nicotine			0.391
Yes	19 (38)	31 (31)	
No	31 (62)	69 (69)	
Opium			0.618
Yes	6 (12)	15 (15)	
No	44 (88)	85 (85)	
Cannabis			0.466
Yes	4 (8)	5 (5)	
No	46 (92)	95 (95)	
Amphetamine			0.145
Yes	5 (10)	4 (4)	
No	45 (90)	96 (96)	
RBC (cells/μL)†	4.77 ± 0.52	4.70 ± 0.52	0.467
Hb (g/dL)‡	14.25 ± 1.58	13.85 ± 1.64	0.156
MCV (fL)‡	87.65 ± 3.62	87.16 ± 5.97	0.597
WBC (cells/μL)†	7.49 ± 2.22	7.70 ± 2.76	0.998
Urea (mg/dL)†	30.54 ± 8.22	29.77 ± 8.22	0.280
Creatinine (mg/dL)†	0.93 ± 0.15	0.90 ± 0.13	0.378

Values are presented as mean ± standard deviation or number (%). *Chi-square statistical test was used; †Mann-Whitney statistical test was used; ‡Independent samples t-test statistical test was used. RLS, restless legs syndrome; RBC, red blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; WBC, white blood cell count.

Table 2. Comparison of different drug use histories in people with and without RLS

Medication	RLS		p-value
	Yes (n = 50)	No (n = 100)	
Anticonvulsive			
Sodium valproate†	25 (50)	53 (53)	0.729
Topiramate*	1 (2)	1 (1)	> 0.999
Gabapentin*	5 (10)	3 (3)	> 0.999
Phenobarbital*	1 (2)	2 (2)	0.302
Carbamazepine†	0 (0)	4 (4)	0.072
Lamotrigine*	4 (8)	2 (2)	0.096
SSRI			
Sertraline†	4 (8)	4 (4)	0.304
Benzodiazepine			
Clonazepam†	2 (4)	14 (14)	0.061
Lorazepam†	24 (48)	46 (46)	0.817
Alpha2 agonist			
Clonidine*	1 (2)	1 (1)	> 0.999
Anticholinergic			
Biperiden†	8 (16)	17 (17)	0.877
Antipsychotic			
Haloperidol*	0 (0)	3 (3)	0.551
Quetiapine†	16 (32)	20 (20)	0.105
Olanzapine†	9 (18)	10 (10)	0.165
Aripiprazole†	6 (12)	8 (8)	0.427
Risperidone†	24 (48)	62 (62)	0.102
Clozapine†	6 (12)	14 (14)	0.734
Opioid			
Methadone*	2 (4)	2 (2)	0.601
Mood stabilizer			
Lithium†	22 (44)	24 (24)	0.012
Beta blocker			
Propranolol†	4 (8)	7 (7)	0.825

Values are presented as number (%).
*Fisher's exact test was used; †Chi-square test was used.
RLS, restless legs syndrome; SSRI, selective serotonin uptake inhibitor.

Table 3. Comparison of various psychiatric disorders in people with and without RLS

Psychiatric disorders	RLS		p-value
	Yes (n = 50)	No (n = 100)	
Schizophrenia spectrum and other psychotic disorders			
Schizophrenia*	4 (8)	21 (21)	0.044
Schizophrenia disorder*	2 (4)	7 (7)	0.466
Brief psychotic disorder†	0 (0)	1 (1)	> 0.999
Delusional disorder†	0 (0)	2 (2)	0.553
Unspecified schizophrenia and other psychotic disorder†	5 (2)	5 (5)	0.664
Manic episode with psychotic feature†	1 (2)	4 (4)	0.655
Bipolar and related disorders			
Bipolar 1 disorder*	32 (64)	53 (53)	0.200
Bipolar 2 disorder†	0 (0)	1 (1)	> 0.999
Depressive disorders			
Major depression disorder*	8 (16)	6 (6)	0.047
Generalized anxiety disorder†	1 (2)	0 (0)	0.333
Mixed anxiety depressive disorder†	1 (2)	0 (0)	0.333
Trauma and stressor related disorder			
Posttraumatic stress disorder†	0 (0)	1 (1)	> 0.999
Adjustment disorder†	0 (0)	2 (2)	0.553
Obsessive-compulsive and related disorders			
Obsessive-compulsive disorder†	1 (2)	0 (0)	0.333
Personality disorders			
Cluster B personality disorder†	3 (6)	4 (4)	0.686
Cluster C personality disorder†	1 (2)	0 (0)	0.333
Neurodevelopmental disorders			
Attention-deficit/hyperactivity disorder†	1 (2)	0 (0)	0.333

Values are presented as number (%).
*Chi-square test was used; †Fisher's exact test was used.
RLS, restless legs syndrome.

Table 4. Logistic regression test to examine the variables affecting the incidence of RLS

Characteristic	Odds ratio (95% CI)	p-value
Lithium	2.836 (1.331−6.046)	0.007
Clonazepam	0.191 (0.039−0.921)	0.039

RLS, restless legs syndrome; CI, confidence interval.

abuse, mean age, or laboratory factors, such as RBC count, Hb, mean corpuscular volume, white blood cell count, urea, or creatinine. On the other hand, the prescription of lithium in the group with RLS was significantly higher than that in individuals without RLS symptoms. Despite the lack of significant differences in clonazepam prescription between the two groups, the use of this drug in the patients without RLS was reported to be relatively more than in the RLS positive group.

In similar study, the prevalence of RLS in patients admitted to psychiatric hospital in Lebanon was 18% [14]. In comparison with healthy individuals, the risk of suicidal ideation or behav-ior (27.1% vs. 7%) or depression history (65.6% vs. 22.8%) in RLS patients was significantly high [15]. In the study conducted by Pullen et al. [16], the prevalence of attention-deficit/hyperactivity disorder (ADHD), mood disturbances, anxiety disorders, and behavioral disturbances in adolescents with RLS were 25%,

29.1%, 11.5%, and 10.9%, respectively. Lee et al. [12] reported that the lifetime prevalence of psychiatric disorders between individuals with RLS was 36.8%, which is significantly higher than subjects without RLS (14.6%). According to our study results, the difference in suicidal ideation rate between individuals with and without RLS was not statistically significant. The mentioned difference in the results can be considered to be due to the small sample size of the present study, and as a result, the impossibility of comparing the frequency of suicidal ideation among different psychiatric disorders, due to the mentioned limitation.

In relation to psychiatric disorders, the prevalence of major depressive disorder in patients with RLS was significantly higher than in patients without RLS. In contrast, the prevalence of schizophrenia in the RLS positive group was significantly lower than in the RLS negative group. Kang et al. [17] examined the clinical pattern and association of RLS with schizophrenia according to the DSM-5 scale. The results of the study show that the prevalence of RLS in individuals with schizophrenia is 21.4%. Also, 47.8% of the RLS positive group had experienced at least one of the symptoms of RLS. The difference between our results and the mentioned study may be attributed to the difference in the target population, because in our study, other patients admitted to a psychiatric hospital were also included in the study.

It seems that the relationship between RLS and psychiatric disorders is bidirectional, wherein all the signs and symptoms of this syndrome, such as sleep disorders and discomfort with numbness in the legs, play a role in the occurrence of distress and predispose the patient to psychiatric disorders [18]. It is important to note that RLS and psychiatric disorders may show similar pathophysiology, and dopamines play a critical role in both RLS and psychiatric disorders [12]. Several studies confirmed that the prevalence of psychiatric disorders, particularly depression, among individuals with RLS was significantly higher than among healthy individuals [18-21]. The prevalence of RLS in the elderly population of France was 8.2%; consistent with the results of our study and, in comparison with healthy individuals, the prevalence major depressive disorder in patients with RLS was significantly increased [22]. Unlike the present study, Lopez et al. [23] reported that the prevalence of RLS among individuals with ADHD was 33%, which was significantly higher than that among healthy individuals without RLS.

The prevalence of panic disorders and DSM-IV major depressive disorder in patients with RLS was 16.7% and 19%, respectively [12,24]. In the study conducted between Korean adults, the adjusted odds ratio for the diagnosis of DSM-IV major depressive disorder, panic disorder, and posttraumatic stress disorder were 2.57%, 18.9%, and 3.76%, respectively [25]. Agüera-Ortiz et al. [6] reported that the prevalence of RLS among individuals admitted to a Spanish psychiatric clinic was 11%. These results indicate the strong association between RLS and DSM-IV depression and anxiety disorders. Tully et al. [22] showed an association between generalized anxiety disorder (GAD) and co-

morbid GAD−depression disorder with probable RLS. Although several studies have indicated that patients with RLS might be depressed because of difficulty falling asleep and staying asleep, the association between RLS and major depressive disorder or dysthymia was not confirmed [26]. In line with the aforementioned studies, the difference between individuals with and without RLS in terms of major depressive disorder was statistically significant. However, the association between GAD or posttraumatic stress disorder and RLS was not significant. The difference may be attributed to the small sample size and lack of diagnosis of GAD and posttraumatic stress disorder in our study.

There is a little knowledge about the relationship between RLS and suicidal thoughts. Several studies indicate that the risk of suicide in individuals with RLS was increased [14,15,24]. Zhuang et al. [27] found that the risk of suicide in patients with RLS was 2.66 higher than in individuals without RLS. Para et al. [15] showed that in RLS individuals, the lifetime risk of suicidal ideation or behavior and depression history was significantly higher than in healthy participants. However, in the present study, no significant difference in terms of suicidal thoughts was observed between the individuals with and without RLS. This difference may be attributed to the small sample size and lack of comparison of the frequency of suicidal ideation among different psychiatric disorders, due to the mentioned limitation.

Several studies have confirmed the relationship between antidepressants prescription and RLS [28-31]. A cross-sectional study of 18980 individuals with selective serotonin reuptake inhibitor (SSRI) drugs prescription found that the symptoms of RLS following medication use increased and intensified [32]. Several studies confirmed the relationship between lithium prescription and RLS [33,34], while other studies confirmed the relationship between treatments with amitriptyline, mirtazapine, and multiple SSRIs and higher frequency of PLMS [35,36]. In line with these studies, our results indicate that lithium prescription could increase the risk of RLS occurrence. However, the relationship between other antidepressant drugs prescription and RLS was not significant.

Although our research is the first study of RLS prevalence in patients with psychiatric disorders in Iran, as with any study, there were limitations. These limitations include the low sample size, lack of prospective examination, and lack of separate examination in various psychiatric disorders; the use of the RLS diagnosis questionnaire to evaluate RLS in psychiatric patients; the lack of research on some medical conditions affecting RLS; and the cross-sectional design that limits the investigation of causal effects.

In conclusion, the results of the present study show significant associations between the prescription of some psychiatric medication, as well as psychological disorders, and RLS. Therefore, given the numerous complications of RLS and its negative effects on the quality of life, routine screening and evaluation of these patients can help better manage psychological disorders. The re-

sults of the present study will help researchers to fill part of the information gap in this area. To better evaluate and improve the prognosis of patients, consultation with sleep disorders specialists is recommended.

Author Contributions

Conceptualization: Mahboubeh Eslamzadeh. Data curation: Tina Ansari Ram. Formal analysis: Aazam Sadat Heydari Yazdi. Funding acquisition: Maryam Emadzadeh. Investigation: Azade Heydarzade Mohamadrezakhan. Project administration: Mahboubeh Eslamzadeh. Writing—original draft: Azade Heydarzade Mohamadrezakhan. Writing—review & editing: Azade Heydarzade Mohamadrezakhan.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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