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The Relationship between Restless Leg Syndrome Severity with Neuropsychological Performance and Menstrual Disorders in Young Women

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ABSTRACT

Background & aim: Restless leg syndrome (RLS) is a frequent sensory dyskinesia disorder of the nervous system and a cause of disability in several aspects. This study aimed to determine the relationship between RLS and mood complications, menstrual patterns, and its associated symptoms among young women.

Methods: This cross-sectional study was undertaken on 118 female university students in Birjand, Iran, from December 2019 to January 2020 using a multistage cluster sampling method. The degree of RLS was assessed using the International RLS Severity Scale. The severity of PMS was characterized via the Premenstrual Syndrome Screening Tool (PSST). Neuropsychological performance of participants was evaluated. Data analysis was performed by SPSS software (version 16.0).

Results: Of 118 participants, 29.7%, 32.2%, 27.9%, and 10.2% of them were not affected by RLS or suffered from mild, moderate, or severe types of RLS, respectively. The subjects with RLS had a significantly lower duration of their menstruation cycle and higher PSST scores compared to those without it. Subjects with different severities of RLS scored higher for the severity of depression, anxiety, stress, insomnia, and sleepiness than normal women ($P<0.01$). The RLS score was a significant factor related to the scores for cognitive abilities ($\beta=-0.33$; $P=0.022$), depression ($\beta=0.32$; $P=0.001$), anxiety ($\beta=0.24$; $P=0.003$), stress ($\beta=0.44$; $P<0.001$), quality of life ($\beta=-0.23$; $P<0.001$), insomnia ($\beta=0.21$; $P=0.001$), sleepiness ($\beta=0.15$; $P=0.014$) and PSST ($\beta=0.28$; $P=0.019$).

Conclusion: In the absence of health management, RLS is potentially associated with depression, anxiety, sleep disruption, cognitive impairment, decreased quality of life, and menstrual problems.

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Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder typically characterized by paresthesia and an uncontrollable urge to move the extremities, especially the legs, with symptoms that worsen at rest or during the night and are partially or entirely alleviated by movement or by walking (1). RLS, as a complex disorder, may be related to primary, or secondary to other conditions. The main theories for the cause of RLS have suggested a pathogenesis that includes a genetic susceptibility (2), brain iron deficiency (3), and central nervous system dopamine imbalance (4-5).

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The prevalence of RLS is found to be 5-15% in adults and 2-4% in children and adolescents (6, 7). RLS is approximately 50% more frequent in women, and this may be because it is associated with increased levels of estrogen or neuropsychological alterations (8). There may be a bidirectional association between RLS and comorbid psychological distress such as depression (9-11). RLS has a profoundly detrimental effect on sleep; many patients with RLS suffer from chronic insomnia. There is a bi-directional relationship between sleep disorders and depression; insomnia is known as a manifestation of depression, but it also increases risk of predisposing to depressive moods, which have been related to cognitive decline (12-13). However, the results of the few studies about cognitive performance are conflicting (14-15). This evidence indicates that RLS patients are possibly more susceptible to neuropsychological complications.

On the other hand, in women of reproductive age, weekly and monthly hormonal fluctuations are related to the menstrual cycle. Menarche describes the first menstrual cycle and it is one of the striking events in female puberty; women of childbearing age are commonly affected by symptoms associated with menstrual disturbances such as menstrual irregularities, primary dysmenorrhea (PD) as well as premenstrual syndrome (PMS) (16-17).

PMS is a group of physical and psychological complaints that women experience one week before the onset of menstruation. PD is characterized by painful cyclic cramps in the lower abdomen that happen with menstruation without organic pathology (18).

RLS symptoms fluctuate with the changing levels of estrogen in women. Within the menstrual cycle, estrogen concentrations vary significantly, and aggravation of RLS symptoms during the menstrual period was reported in 29% of RLS cases (19-20). Goecke et al. (2020) have recently reported that the degree of RLS ($r=0.26$, $P<0.01$) correlated with the severity of PMS (21). It has also been shown that PD patients have a higher prevalence of RLS than those without it. During menstruation, the release of prostaglandins by the endometrium causes an elevation in the amount and intensity of contractions in the uterus, leading to hypoxia and ischemia in the uterine muscles and consequently menstrual-associated pain. This increment in prostaglandin concentrations may implicate sleep complications, including RLS in PD (22). There have been reports of an association between RLS and menstrual pain disorders (20, 23), but no definitive underlying mechanism of this association has been found. Additionally, there is accumulating evidence supporting the strong association between menstrual-associated pain and neuropsychological complications such as depression, aggression, sleep disorders, and poor quality of life (QoL) in women. Previous studies also indicated the possibility of psychiatric comorbidity of PMS with panic disorder, mood, and anxiety states (18, 24-25).

The concurrent occurrence of psychological disorders related to PMS or menstrual problems possibly increases the adverse consequences of RLS and can be deleterious for the female's physical and mental health.

The relationship between RLS, psychopathological states, and menstrual-corresponding problems in young women has not been comprehensively investigated previously. On the other hand, menstrual-associated complications are usually considered physiological pain and ignored by women. Regarding clinical relevance, psychological factors may be implicated in unsuccessful RLS treatment outcomes, as found, for instance, in other chronic pain states (26). Since the female side of RLS seems entirely momentous, this study aimed to determine the relationship between RLS and mood complications, menstrual patterns, and its associated symptoms among young women.

Materials and Methods

This cross-sectional survey was conducted on young women living in Birjand city, Khorasan Province, Iran, from December 2019 to January 2020 (27). The Ethical Committee of Birjand University of Medical Sciences confirmed the study (Code: IR.BUMS.REC.1398.160).

The sample size needed to achieve 80% power and $\alpha' = 0.05$ (z value of 1.96) was calculated according to results from a former study ($r=0.28$ between RLS with DASS-21 score) by PASS software (NCSS, Kaysville, UT, USA) (28).

Concerning these assumptions at least 110 participants were essential.

The inclusion criteria were: young females, aged between 18-24 years, having a normal menstrual cycle, being single (unmarried), and providing written informed consent. The exclusion criteria were any acute or chronic disorders, particularly gynecological disorders, and taking any drug. Participants were chosen from five universities in Birjand using a multistage cluster sampling approach. In the first stage, a total of five out of 22 universities were randomly identified, and one class from each academic department (3 classes from each university) was randomly chosen for inclusion. In each class, nearly 10 students are randomly selected based on their student ID number. Universities, classes, and students were selected using computer-generated random numbers. All students in the selected classes (n = 150) were invited to participate in the research, and 118 (79%) met the inclusion criteria and were accepted to participate, making a final sample size of 118.

Demographic information of the participants was collected through face-to-face interviews. Anthropometric parameters, i.e., weight, height, waist, and hip circumference, were measured through excellently validated instruments and a standard protocol. Weight was measured wearing the least clothes and without shoes via a Seca digital scale. The height was record using a fixed measuring tape on the wall on standing position without shoes. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Waist circumference was assessed using a flexible tape measure from the narrowest point between the lowest rib and the iliac crest. Waist-to-hip ratio was obtained by dividing the waist circumference by the hip circumference. Hip circumferences were measured at the level of the anterior superior iliac spine, where this could be felt, in a different way at the broadest circumference below the waist.

The clinical diagnosis of RLS was based on the National Institutes of Health's recommended diagnostic criteria for RLS, which is made up of four parts (29). Moreover, the severity of the symptoms of RLS was judged by using the validated International RLS Severity Scale (30-31). This questionnaire includes 10 items: 5 items pertain to symptom frequency and severity, and 5 items address the impact of bothering manifestations on aspects of daily life activities. The respondent rates each question on a scale of 0 to 4 for the last week, with scores ranging from 0 to 40. Due to the small sample size, subjects were categorized as severe/very severe (scores >21), moderate (score=10–20), mild (score=1-10), and none (score=0). The International RLS Study Group assessed the RLS Questionnaire's reliability, and its Cronbach's alpha was declared to be 0.93-0.98 (31). The reliability of the Persian language version of the RLS screening questionnaire has been confirmed by several studies; for instance, in the study by Habibzade et al. (2011) the content validity was estimated by ten experts and the reliability of the tool was accepted (Cronbach's alpha coefficient of 0.97) (32).

Standard questionnaires were used to assess features of menstruation, which included menarcheal age, menstrual pattern (regularity of menstrual cycle, cycle length, and average days of bleeding), the most common menstruation-associated physical symptoms, and the presence of PMS and/or PD (33).

A diagnosis of PD was based on these criteria: pain initiating within the first hours of menstruation, low abdominal pain related to the beginning of menarche, and lengthening for 8–72 hours. PD may be characterized by backaches, nausea, vomiting, and breast tenderness (34).

Premenstrual Symptoms Screening Tool (PSST) is a reliable and valid self-report questionnaire that was developed in 2003 for the screening of PMS cases (35). The PSST includes 19 items, and each question is rated on a 4-point scale scored from 0 to 3 ("none", "mild", "moderate," and "severe," respectively), obtaining a total score range of 0 to 57. This instrument was validated with reliability, internal consistency, and validity of 0.9, 0.8, and 0.7, respectively, for the Iranian population (36).

The negative emotional status of participants was estimated by using the brief version of the Depression, Anxiety, and Stress Scale (DASS-21). The DASS-21 includes 21 items on a 4-point Likert scale (score: 0 to 3), subdivided into 3 subsections of 7 questions, corresponding to depression, anxiety, and stress. The final score

of each subsection should be doubled. The valid and reliable Persian version of this questionnaire was used in this study (Cronbach's alpha was confirmed at 0.7, 0.66, and 0.76 for depression, anxiety, and stress, respectively)(37).

The Cognitive Abilities Questionnaire (CAQ) captures the composite dimension of cognitive performance. The CAQ includes 30 questions with total scores ranging from 30 to 150 based on a 5-point Likert scale (1–5). Higher scores showed better cognitive functions (38). The CAQ asks about seven domains, including memory, inhibitory control and selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility. The validity of the questionnaire and internal consistency (Cronbach's alpha =0.83) and good test-retest reliability (r=0.86) have been reported for Iranian subjects (38).

Daytime sleepiness: excessive daytime somnolence was evaluated using the Epworth Sleepiness Scale (ESS). This is a validated and reliable questionnaire that includes eight items that explore the probability of dozing in eight different conditions. Snoozing likelihood ratings range from 0 (no) to 3 (high probability). Only five minutes are required to complete the ESS. Possible scores vary from 0 to 24, with higher scores indicating greater odds of daytime sleepiness. Haghighi et al. confirmed the validity and reliability of ESS for Iranian population (Cronbach's alpha=0.8 and intra-class correlation coefficient=0.8) (39).

Insomnia status: Insomnia is described by a subjective feeling of short, unsatisfying sleep despite the ability to fall asleep. The Insomnia Severity Index (ISI) is a seven-item questionnaire assessing insomnia intensity (i.e., difficulties falling asleep) during the preceding two weeks. Each item is scored using a five-point Likert scale ranging from '0' (absence) to '4' (very much). The calculation of the total score was based on summing the seven questions for a possible total score ranging from 0 to 28. The ISI was validated in the Iranian population (Cronbach's alpha >0.8 and intra-class correlation coefficient >0.7) (40). Higher scores indicate the probable presence of an insomnia disorder.

The physical and mental aspects of QoL were explored using a 12-item short-form health survey (SF-12), which 12 items that encompassed eight different domains. Elevated scores indicate superior health-related QoL. The Persian version of the SF-12 with favorable reliability and validity was used for this study (Cronbach's α=0.72 and intra-class correlation coefficient=0.74)(41).

Statistical analyses were done using SPSS for Windows version 16.0. A Kolmogorov–Smirnov test was recruited to assess whether the data were normally distributed. All of the evaluated variables that were normally distributed were analyzed using parametric tests. For statistical analysis, participants were classified into four groups according to the degree of RLS. Continuous variables are demonstrated as mean ± SD and compared between four groups by using one-way ANOVA and post hoc Tukey's test. Categorical variables are shown as a number (percentage) and compared between four categories by the Chi-square test. The correlation between variables was explored using Spearman's correlation coefficient analysis. Linear regression analysis was applied to judge the effects of RLS scores on neuropsychological performance tasks and PSST scores as the dependent variables. A P value < 0.05 was set as statistically significant.

Results

118 subjects with a mean age of 20.6±1.7 years were included in the study. Among subjects, 89% of them lived in the dormitory, and 1.16% lived in the village. 50.5% of students were studying in the fields of medical sciences, of which 72.2% were at the undergraduate level, 1.16% at the postgraduate level, and 11.7% were in general medicine.

Finally, 35 (29.7%), 38 (32.2%), 33 (27.9%), and 12 (10.2%) of the participants did not have RLS or were affected by mild, moderate, and severe/very severe types of RLS, respectively. There was no considerable difference in age, BMI, and waist: hip ratio (WHR) between different categories of RLS among the study population (P>0.05) (Table 1).

Table 1. Anthropometric indices in research samples

Variables	RLS				F	P-Value
	No (N=35)	Mild (N=38)	Moderate (N=33)	Severe/Very Severe (N=12)		
Age (year)	20.88±1.30	20.67±1.63	20.69±1.64	21.83±2.12	1.75	0.160
BMI (kg/m^2)	21.52±2.34	21.26±3.72	20.46±2.20	20.11±3.95	1.15	0.330
WHR	0.73±0.03	0.75±0.04	0.73±0.03	0.72±0.04	2.30	0.081

One-way ANOVA and post hoc Tukey's test were performed. BMI: body mass index; RLS: restless legs syndrome; WHR: waist: hip ratio

The features of the menstrual cycle (menstrual age, cycle length, duration of flow), PSST score, presence of PD, as well as menstrual associated symptoms, about the presence and severity of RLS, are reported in Table 2. One-way ANOVA and post hoc Tukey's tests showed that the duration of the menstruation cycle was significantly different between the group without RLS and the mild RLS group (p=0.020). Also, in the severe/very severe RLS group, the mean pain intensity of the PSST was less in the non-RLS group (P=0.044). No significant difference was detected between groups with different severity of RLS in terms of menarcheal age, days of bleeding, presence of PD, and physiological symptoms of PMS (P>0.05).

Table 2. The relationship of menstrual pattern, PSST score, and physiological symptoms with restless legs syndrome in research samples

Variables	RLS				Test results	P-Value
	No (N=35)	Mild (N=38)	Moderate (N=33)	Severe/Very severe (N=12)		
Age at menarche (year)	13.34±1.21	13.05±1.54	13.27±1.46	13.25±0.86	F=0.29	0.831
Average duration of bleeding (d)	6.51±1.31	6.78±1.03	6.63±1.38	6.58±1.16	F=0.29	0.829
Duration of the menstruation cycle (d)	30.01±6.12	26.53±4.91	28.47±3.32	28.23±3.26	F=3.39	**0.020** α
PSST score	19.51±2.17	22.36±10.24	23.06±9.91	29.50±18.63	F=3.24	**0.025** β
Dysmenorrhea, yes	24(68.6)	26(68.4)	24(72.7)	10(83.3)	X^2=1.75	0.643
Menstruation-associated physical symptoms, N (%)						
Tender breasts	18(51.4)	23(60.5)	12(36.4)	5(41.7)	X^2=4.46	0.215
Backache	24(68.6)	32(82.2)	29(87.9)	11(91.7)	X^2=5.74	0.125
feeling of bloating	30(85.7)	35(92.1)	26(78.8)	10(83.3)	X^2=2.59	0.457
Weight gain	17(48.6)	16(42.1)	9(27.3)	4(33.3)	X^2=3.57	0.312
Swelling of the limbs	12(34.3)	10(26.3)	11(33.3)	6(50.0)	X^2=2.36	0.501
joint or muscle pain	22(62.9)	25(65.8)	23(69.7)	10(83.3)	X^2=1.84	0.606
Gastrointestinal symptoms	22(62.9)	23(60.5)	20(60.6)	10(83.3)	X^2=2.30	0.511

*By using One-way ANOVA and post hoc Tukey's test or chi-square test as appropriate.
α Significance between the No RLS group and Mild group
β Significance between the No RLS group and Severe/very severe group LS

Results from one-way ANOVA test indicated that on most of the cognitive ability questionnaires, the normal subjects scored more favorably than those with severe/very severe RLS (P<0.05). The score of QoL reduced with the elevating severity of RLS (P<0.001).

Subjects with different degrees of severity of RLS scored significantly worse than normal cases for depression, anxiety, stress, and severity of insomnia and sleepiness (P<0.01). Although there were no significant differences in nocturnal sleep hours between these four groups (P=0.523) (Table 3).

Table 3. The relationship between neuropsychological function and RLS in research samples

Variables	RLS				F	P-Value*
	No (N=35)	Mild (N=38)	Moderate (N=33)	Severe/very severe (N=12)		
Test of cognitive abilities						
Memory	26.62±2.83	26.87±2.70	26.12±3.15	22.84±4.82	1.22	**0.002**$^{\alpha, \beta, \gamma}$
Inhibitory control and selective attention	22.53±3.91	23.38±3.86	22.72±3.64	19.67±3.75	3.00	**0.034**$^{\beta}$
Decision making	20.25±3.48	20.31±3.75	18.93±3.36	16.41±4.37	4.33	**0.006**$^{\alpha, \beta}$
Planning	11.62±2.67	11.52±2.25	11.52±2.48	10.31±2.36	0.97	0.412
Sustain attention	10.01±2.28	10.30±2.4	9.73±2.49	8.01±2.32	3.09	**0.030**$^{\alpha, \beta}$
Social cognition	10.21±2.08	10.54±2.36	10.81±2.68	11.12±2.22	0.72	0.545
Cognitive flexibility	14.65±2.53	15.13±3.16	15.18±2.50	14.27±3.03	0.53	0.661
Total cognitive ability task	115.10±12.54	117.7±14.2	115.01±11.89	102.4±14.63	4.27	**0.007**$^{\alpha, \beta, \gamma}$
Dass-21						
Depression	8.45±8.13	8.69±8.2	10.43±9.21	19.07±11.88	4.77	**0.004**$^{\alpha, \beta, \gamma}$
Anxiety	6.73±6.58	6.52±5.27	8.53±7.75	14.50±11.41	4.29	**0.007**$^{\alpha, \beta}$
Stress	11.85±8.12	14.22±9.09	17.76±8.94	26.23±7.67	9.06	**<0.001**$^{\alpha, \beta, \gamma, \delta}$
Quality of life (SF-12)						
Physical health	16.84±1.92	16.38±1.89	15.72±2.13	13.64±2.95	7.90	**<0.001**$^{\alpha, \beta, \gamma}$
Mental health	18.20±3.27	17.83±3.27	16.18±3.19	15.08±3.25	4.85	**0.003**$^{\alpha, \delta}$
SF-12 score	35.13±4.69	34.10±4.37	31.81±4.58	28.79±4.72	7.61	**<0.001**$^{\alpha, \beta, \delta}$
Test of sleep pattern						
Insomnia score (ISI)	1.88±3.57	4.18±5.26	5.2±5.97	9.05±7.29	5.85	**0.001**$^{\alpha, \beta}$
Daytime sleepiness score (ESS)	1.93±4.23	4.86±5.53	6.1±5.82	6.31±5.26	4.04	**0.009**$^{\delta}$
Nocturnal sleep hours	8.43±1.07	7.98±1.55	8.2±1.64	8.01±1.16	0.75	0.523

Data presented as mean ± SD *By using one-way ANOVA. The significance of bold values is P<0.05. $^{\alpha}$ Significance between the No RLS group and the Severe/very severe group $^{\beta}$ Significance between Mild RLS group and Severe/very severe group $^{\gamma}$ Significance between the Moderate RLS group and Severe/very severe group $^{\delta}$ Significance between the No RLS group and Moderate group

Correlation analysis indicated that RLS scores were positively related to scores of depression, anxiety, stress, insomnia, sleepiness, and PSST. An inverse association was found between the RLS score and cognitive abilities and QoL. These findings are shown in Table 4.

The relationship between the RLS score and the scores on the PSST and neuropsychological performance tests were examined using both univariate and multivariate linear regression analysis. This revealed that RLS scores were significant factors in the multivariate model associated with cognitive abilities, depression, anxiety, stress, QoL, insomnia, sleepiness, and PSST scores (P<0.05).

Table 4. Correlation matrix between RLS score and neuropsychological tests of research samples

Variables	RLS score							
Cognitive abilities								
r	-0.25							
p	0.006	Cognitive abilities						
Depression								
r	0.33	0.50						
p	<0.001	<0.001	Depression					
Anxiety								
r	0.29	0.43	0.64					
p	0.001	<0.001	<0.001	Anxiety				
Stress								
r	0.45	0.45	0.64	0.60				
p	<0.001	<0.001	<0.001	<0.001	Stress			
Quality of life								
r	-0.43	-0.57	-0.57	-0.42	-0.58			
p	<0.001	<0.001	<0.001	<0.001	<0.001	Quality of life		
Insomnia								
r	0.34	0.26	0.18	0.22	0.35	-0.32		
p	<0.001	0.004	0.045	0.015	<0.001	<0.001	Insomnia	
Daytime sleepiness								
r	0.24	0.24	0.09	0.18	0.27	-0.18	0.63	
p	0.008	0.009	0.320	0.047	0.003	0.045	<0.001	Daytime sleepiness
PSST score								
r	0.27	-0.42	050	0.43	0.49	-0.42	0.26	0.24
p	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	0.009

Discussion

In a cross-sectional survey, we investigated the relationship between RLS and mood complications, menstrual patterns, and its associated symptoms among young women. There were two important findings. First, compared to representative values, women with RLS had neuropsychological dysfunction in the domains of memory, inhibitory control, selective attention, decision making, sustained attention, depression, anxiety, stress, insomnia, and daytime sleepiness. Second, women with RLS suffered more from menstrual problems and severe PMS symptoms. The novel findings of this study included the psychological distress and menstrual problems suffered by women with RLS; to our knowledge, no other study has evaluated the whole spectrum of these abnormalities in subjects with RLS.

RLS is the most common type of sensory dyskinesia that affects the nervous system. It is also a major cause of disability. We found that increasing the severity of RLS was related to increasing scores for depression, anxiety, stress, insomnia, and sleepiness. Castillo et al. (2014) found that the frequency of depression, aggression, and stress was nearly three times higher in RLS subjects compared to the general population (28). Untreated RLS subjects presented greater psychological distress in the areas of somatization and compulsivity than matched controls (42). On the other hand, it has been shown that cases with both depression and RLS had a greater vulnerability to developing insomnia (43).

Sleep disturbance was another problem observed among subjects with RLS. RLS may have an etiological cause or simply be accompanied by other sleep issues; insomnia and poor sleep quality can result in daytime snoozing and psychological distress.

In several pathologic conditions, the presence of RLS also aggravates mood disorders. RLS patients endure higher degrees of disability, fatigue, and sleep disorders, i.e., high sleep latency, decreased sleep duration, and poorer sleep efficiency (44). RLS cases had higher

scores of anxiety and depression and less QoL in cancer patients versus those without RLS (45). Individuals without RLS had lower scores for anxiety, emotion-oriented coping, insomnia, and daytime sleepiness, as well as an elevated quality of sleep, than subjects with RLS in hemodialysis patients (46-48).

The relationship between RLS symptoms and depression or anxiety is not entirely attributed to disturbed sleep; sleep-independent mechanisms are possibly involved in this association too. Insomnia is a causal factor for depression and stress, and RLS leads to insomnia (49). Exhaustion, social seclusion, helplessness, and pain are prevalent in RLS, and these complications may make subjects vulnerable to mood disorders. It is reasonable to speculate that the absence of a suitable remedy for RLS may also cause aggression, stress, anxiety, depression, and disruption of sleep patterns.

The degree of RLS, particularly the frequency of symptoms, negatively affected all aspects of QoL. The lower QoL found in women who suffered from RLS in the current study is inconsistent with previous research (45, 50-52). In a population-based study in the United States, the SF-36 instrument was used for the evaluation of the burden of RLS on QoL. Each of the SF-36 measures in RLS person was remarkably lower than general population norms (52). RLS affects social lives and the emotional and neuropsychological health of individuals (50). Happe and colleagues (2009) also reported that anxiety and depression significantly contributed to the decrement of QoL in RLS patients (53).

In this study, subjects with RLS obtained lower scores for most of the cognitive ability tasks than those without it. Along with us, Pearson and co-workers reported that untreated RLS patients have partial cognitive deficits. The RLS individuals showed lower ability in the Trail Making Test or category verbal fluency test than healthy controls (54). In patients with Parkinson's disease, RLS individuals had significantly worse cognitive function versus controls (55).

This is the first study investigating menstrual patterns and characteristics associated with RLS. RLS subjects have a significantly lower duration of the menstrual cycle and higher PSST scores.

Previously, it has been reported that one-third of premenopausal women with RLS endure symptom exacerbation during menses (19, 56). The prevalence of RLS symptoms in 11-27% of pregnant women also motivated others to query the relevance of women's hormonal factors, especially in connection to the elevation of estrogen values within late pregnancy (20, 57).

Although, during pregnancy, the relationship between hormonal alterations and aggravated RLS is unclear because estrogen concentrations decrease before menses (58). In contrast, iron depletion during menstrual blood loss may be a more probable reason for this result. Additionally, RLS was observed to be elevated in blood donors (59-60). On the other hand, psychological comorbidity with RLS is also connected to altered changes in pain thresholds and can potentially predict future pain (61-62). We speculated that mood disorders, a common complication of RLS, are also a risk factor for PMS pain severity.

This study is the first to highlight the possibility that RLS may be related to psychological problems and menstrual-associated complaints. The cross-sectional nature of the current survey prevents any inferences concerning causality in RLS, psychological distress, and menstrual-associated problems. We mostly relied on the RLS questionnaire scores instead of a diagnosis from a clinician. Indeed, we did not use objective tools for assessment of QoL, depression, anxiety, stress, and sleep problems, but relied on participants reporting their symptoms; however, SF-12, DASS-21, ISI, and ESS are reliable and valid instruments for measurement of these symptoms. Additional proper instruments should be applied in future research to evaluate the cognitive performance of RLS. In the clinical setting, our findings may broaden our knowledge of the complex relationships between neuropsychological function and menstruation with respect to RLS. We would suggest that future studies should encompass a prospective design, various risk factors, and a larger sample size.

Conclusion

In the absence of mitigating interventions, a consequence of RLS is depression, anxiety, increased insomnia, daytime snoozing, cognitive impairment, decreased QoL, and menstrual problems. Treatment of RLS has the promise of improving clinical outcomes, which would affect one's participation in daily functions.

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Conflicts of interest

The authors declared no conflicts of interest.

References

1. Guay A, Houle M, O'Shaughnessy J, Descarreaux M. Current Evidence on Diagnostic Criteria, Relevant Outcome Measures, and Efficacy of Nonpharmacologic Therapy in the Management of Restless Legs Syndrome (RLS): A Scoping Review. Journal of Manipulative and Physiological Therapeutics. 2020; 43(9):930-941.
2. Birinyi PV, Allen RP, Hening W, Washburn T, Lesage S, Earley CJ. Undiagnosed individuals with first-degree relatives with restless legs syndrome have increased periodic limb movements. Sleep Medicine. 2006; 7(6): 480-485.
3. Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. Journal of Sleep Research. 2005; 14(1): 43-47.
4. Sethi KD, Mehta SH. A clinical primer on restless legs syndrome: what we know, and what we don't know. American Journal of Managed Care. 2012; 18(5 Suppl): S83-S8.
5. Braga-Neto P, da Silva-Júnior FP, Monte FS, de Bruin PF, de Bruin VM. Snoring and excessive daytime sleepiness in Parkinson's disease. Journal of the Neurological Sciences. 2004; 217(1): 41-45.
6. Yilmaz K, Kilincaslan A, Aydin N, Kor D. Prevalence and correlates of restless legs syndrome in adolescents. Developmental Medicine & Child Neurology. 2011; 53(1): 40-47.
7. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents—the Peds REST study. Pediatrics. 2007; 120(2): 253-266.
8. Araujo SMHA, de Bruin VMS, Nepomuceno LA, Maximo ML, de Francesco Daher E, Ferrer DPC, et al. Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Medicine. 2010; 11(8): 785-790.
9. Cuellar NG, Strumpf NE, Ratcliffe SJ. Symptoms of restless legs syndrome in older adults: outcomes on sleep quality, sleepiness, fatigue, depression, and quality of life. Journal of the American Geriatrics Society. 2007; 55(9): 1387-1392.
10. Szentkiralyi A, Völzke H, Hoffmann W, Baune BT, Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. Psychosomatic Medicine. 2013; 75(4): 359-365.
11. Lee HB, Hening WA, Allen RP, Kalaydjian AE, Earley CJ, Eaton WW, et al. Restless legs syndrome is associated with DSM-IV major depressive disorder and panic disorder in the community. The Journal of Neuropsychiatry and Clinical Neurosciences. 2008; 20(1): 101-105.
12. Kim KW, Yoon IY, Chung S, Shin YK, Lee SB, Choi EA, et al. Prevalence, comorbidities and risk factors of restless legs syndrome in the Korean elderly population–results from the Korean Longitudinal Study on Health and Aging. Journal of Sleep Research. 2010; 19(1-Part-I): 87-92.
13. Szentkiralyi A, Molnar MZ, Czira ME, Deak G, Lindner AV, Szeifert L, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. Journal of Psychosomatic Research. 2009; 67(2): 173-180.
14. Lee HB, Ramsey CM, Spira AP, Vachon J, Allen R, Munro CA. Comparison of cognitive functioning among individuals with treated restless legs syndrome (RLS), untreated RLS, and no RLS. The Journal of Neuropsychiatry and Clinical Neurosciences. 2014; 26(1): 87-91.
15. Kim SM, Choi JW, Lee C, Lee BU, Koo YS, Kim KH, et al. Working memory deficit in patients with restless legs syndrome: an event-related potential study. Sleep Medicine. 2014; 15(7): 808-815.
16. McPherson ME, Korfine L. Menstruation across time: menarche, menstrual attitudes, experiences, and behaviors. Women's Health Issues. 2004; 14(6): 193-200.
17. Bahrami A, Bahrami-Taghanaki H, Afkhamizadeh M, Avan A, Mazloum Khorasani Z, Esmaeili H, et al. Menstrual

disorders and premenstrual symptoms in adolescents: prevalence and relationship to serum calcium and vitamin D concentrations. Journal of Obstetrics and Gynaecology. 2018; 38(7): 989-995.
18. Bahrami A, Sadeghnia H, Avan A, Mirmousavi SJ, Moslem A, Eslami S, et al. Neuropsychological function in relation to dysmenorrhea in adolescents. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017; 215(2017): 224-229.
19. Ghorayeb I, Bioulac B, Scribans C, Tison F. Perceived severity of restless legs syndrome across the female life cycle. Sleep Medicine. 2008; 9(7): 799-802.
20. Hwang S, Shin Y-W, Jung K-Y. Symptom aggravation in restless legs syndrome during menstrual cycle. Journal of Sleep Medicine. 2019; 16(2): 109-112.
21. Goecke TW, Schnakenberg P, Frensch M, Chechko N. Restless legs syndrome during pregnancy and 12 weeks postpartum and its links to cardiovascular diseases, stressful life events, and psychiatric history. Journal of Clinical Medicine. 2020; 9(9): 3046.
22. Çaltekin İ, Hamamcı M, Demir Çaltekin M, Onat T. Evaluation of sleep disorders, anxiety and depression in women with dysmenorrhea. Sleep and Biological Rhythms. 2021; 19(1): 13-21.
23. Uekata S, Kato C, Nagaura Y, Eto H, Kondo H. The impact of rotating work schedules, chronotype, and restless legs syndrome/Willis-Ekbom disease on sleep quality among female hospital nurses and midwives: A cross-sectional survey. International Journal of Nursing Studies. 2019; 95(2019): 103-112.
24. Kamel DM, Tantawy SA, Alsayed N, Bekhet AH, Elbkery N, Khairy A. The relationship between premenstrual syndrome and the quality of sleep among egyptian women: An observational study. Archives of the Balkan Medical Union. 2021; 56(2): 172-178.
25. Prabhavathi K, Kumar TG, Hemamalini R, Poornima K, Saravanan A. Study of psychological predictors and sleep quality in different grades of premenstrual syndrome. National Journal of Physiology, Pharmacy and Pharmacology. 2018; 8(3): 353-357.
26. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Archives of Internal Medicine. 2003; 163(20): 2433-2445.
27. Ayadilord M, Mahmoudzadeh S, Hoseini ZS, Askari M, Rezapour H, Saharkhiz M, et al. Neuropsychological function is related to irritable bowel syndrome in women with premenstrual syndrome and dysmenorrhea. Archives of Gynecology and Obstetrics. 2020; 302(4): 1-9.
28. Castillo PR, Mera RM, Fredrickson PA, Zambrano M, Del Brutto VJ, Del Brutto OH. Psychological distress in patients with restless legs syndrome (Willis-Ekbom disease): a population-based door-to-door survey in rural Ecuador. BMC Research Notes. 2014; 7(1): 1-5.
29. 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 Medicine. 2014; 15(8): 860-873.
30. Wunderlich GR, Evans KR, Sills T, Pollentier S, Reess J, Allen RP, et al. An item response analysis of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Medicine. 2005; 6(2): 131-139.
31. Group IRLSS. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Medicine. 2003; 4(2): 121-132.
32. Habibzade H, Khalkhali H, Ghaneii R. Study of the relationship between restless legs syndrome and sleep disturbance among patients in Critical Care Units. Iranian Journal of Critical Care Nursing. 2011; 4(3): 153-158.
33. Agarwal A, Venkat A. Questionnaire study on menstrual disorders in adolescent girls in Singapore. Journal of Pediatric and Adolescent Gynecology. 2009; 22(6): 365-371.
34. Awed H, El-Saidy T, Amro T. The use of fresh Ginger herbs as a home remedy to relieve primary dysmenorrhea. Journal of Research in Nursing and Midwifery. 2013; 2(8): 104-113.
35. Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. Archives of Women's Mental Health. 2003; 6(3): 203-209.
36. Siahbazi S, Hariri FZ, Montazeri A, Banaem LM. Translation and psychometric properties of the Iranian version of the Premenstrual Symptoms Screening Tool (PSST). Payesh. 2011; 10(4): 421-427.
37. Sahebi A, Asghari MJ, Salari R. Validation of depression anxiety and stress scale (DASS-21) for an Iranian population. Journal of

Iranian Psychologists. 2005;1(4)36-54[In Persioan].
38. Nejati V. Cognitive abilities questionnaire: development and evaluation of psychometric properties. Advances in Cognitive Science. 2013; 15(2): 11-19..
39. Haghighi KS, Montazeri A, Mehrizi AK, Aminian O, Golkhandan AR, Saraei M, et al. The Epworth Sleepiness Scale: translation and validation study of the Iranian version. Sleep and Breathing. 2013; 17(1): 419-426.
40. Yazdi Z, Sadeghniiat-Haghighi K, Zohal MA, Elmizadeh K. Validity and reliability of the Iranian version of the insomnia severity index. The Malaysian Journal of Medical Sciences. 2012; 19(4): 31.
41. Montazeri A, Vahdaninia M, Mousavi SJ, Omidvari S. The Iranian version of 12-item Short Form Health Survey (SF-12): factor structure, internal consistency and construct validity. BMC Public Health. 2009; 9(1): 341.
42. Scholz H, Benes H, Happe S, Bengel J, Kohnen R, Hornyak M. Psychological distress of patients suffering from restless legs syndrome: a cross-sectional study. Health and Quality of Life Outcomes. 2011; 9(1): 73.
43. Lee T-H, Yen T-T, Chiu N-Y, Chang C-C, Hsu W-Y, Chang Y-J, et al. Depression is differently associated with sleep measurement in obstructive sleep apnea, restless leg syndrome and periodic limb movement disorder. Psychiatry Research. 2019; 273(2019): 37-41.
44. Moreira N, Damasceno R, Medeiros C, De Bruin P, Teixeira C, Horta W, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. Brazilian Journal of Medical and Biological Research. 2008; 41(10): 932-937.
45. Ostacoli L, Saini A, Ferini-Strambi L, Castronovo V, Sguazzotti E, Picci RL, et al. Restless legs syndrome and its relationship with anxiety, depression, and quality of life in cancer patients undergoing chemotherapy. Quality of Life Research. 2010; 19(4): 531-537.
46. Chavoshi F, Einollahi B, Haghighi KS, Saraei M, Izadianmehr N. Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. Nephro-Urology Monthly. 2015; 7(2): e24611.
47. Takaki J, Nishi T, Nangaku M, Shimoyama H, Inada T, Matsuyama N, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. American Journal of Kidney Diseases. 2003; 41(4): 833-839.
48. Dikici S, Bahadir A, Baltaci D, Ankarali H, Eroglu M, Ercan N, et al. Association of anxiety, sleepiness, and sexual dysfunction with restless legs syndrome in hemodialysis patients. Hemodialysis International. 2014; 18(4): 809-818.
49. Theofilou PA. Sexual functioning in chronic kidney disease: the association with depression and anxiety. Hemodialysis International. 2012; 16(1): 76-81.
50. Kalloo A, Gamaldo CE, Kwan AB, Salas RE. The impact of restless legs syndrome/willis-Ekbom disorder on quality of life. European Journal of Neurology. 2013; 8(2): 97-104.
51. Svetel MV, Jovic JS, Pekmezovic TD, Kostic VS. Quality of life in patients with primary restless leg syndrome: community-based study. Neurological Sciences. 2015; 36(8): 1345-1351.
52. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, et al. Burden of restless legs syndrome on health-related quality of life. Quality of life research. 2007; 16(4): 617.
53. Happe S, Reese JP, Stiasny-Kolster K, Peglau I, Mayer G, Klotsche J, et al. Assessing health-related quality of life in patients with restless legs syndrome. Sleep Medicine. 2009; 10(3): 295-305.
54. Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome. Sleep Medicine. 2006; 7(1): 25-30.
55. Cederberg KL, Brinkley EB, Belotserkovkaya N, Memon RA, Motl RW, Amara AW. Does restless legs syndrome impact cognitive function via sleep quality in adults with Parkinson's disease. International Journal of Neuroscience. 2020; 130(4): 322-329.
56. Tunç T, Karadağ YS, Doğulu F, İnan LE. Predisposing factors of restless legs syndrome in pregnancy. Movement Disorders. 2007; 22(5): 627-631.
57. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, et al. Restless legs syndrome and pregnancy. Neurology. 2004; 63(6): 1065-1069.
58. Zacur HA. Hormonal changes throughout life in women. Headache: The Journal of Head and Face Pain. 2006; 46(?): S50-SS5.
59. Silber MH, Richardson JW. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. Mayo Clinic Proceedings. 2003; 78(1):52-54.
60. Ulfberg J, Nyström B. Restless legs syndrome in blood donors. Sleep Medicine. 2004; 5(2): 115-118.

61. Kato K, Sullivan PF, Evengård B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. Archives of Internal Medicine. 2006; 166(15): 1649-1654.
62. Ligthart L, Visscher CM, van Houtem CM, Geels LM, Vink JM, de Jongh A, et al. Comorbidity among multiple pain symptoms and anxious depression in a Dutch population sample. The Journal of Pain. 2014; 15(9): 945-955.