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Restless leg syndrome severity in young women is associated with neuropsychological performance and menstrual disorders

Afsane Bahrami (PhD)\(^{1\dagger}\), Masoumeh Askari (MSc)\(^{3, 4}\), Zahra Rajabi (MD)\(^{3}\), Zahra Sadat Hoseini (BSc)\(^{5}\), Gordon A. Ferns (MD, PhD)\(^{5}\)

\(^{1}\) Clinical Research Development Unit, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
\(^{2}\) Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
\(^{3}\) Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
\(^{4}\) Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
\(^{5}\) Department of psychology, University of Birjand, Birjand, Iran

This work was supported by Birjand University of Medical Science (BUMS), Iran.

\(\dagger\)Corresponding authors: Dr. Afsane Bahrami, Clinical Research Development Unit, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Tel: +985137313292, Fax: +9856324380076,

Email: BahramiAF@mums.ac.ir & Afsbahramia931@gmail.com

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Running title: PMS and RLS

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. We aimed to explore the relationship between RLS and mood complications, menstrual patterns and associated symptoms among young women.
Methods: This cross-sectional survey undertaken on 118 female university students in Birjand, Iran in 2020 using a multistage cluster sampling method. The degree of RLS was judged using the International RLS Severity Scale. The severity of PMS was characterized via the Premenstrual Syndrome Screening Tool (PSST). Neuropsychological performance was evaluated by standard questionnaires.

Results: Of the 118 young women, 29.7%, 32.2%, 27.9% and 10.2% of the participants were not affected by RLS, or had, mild, moderate, or severe types of RLS, respectively. The subjects with RLS had 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 severity of depression, anxiety, stress, insomnia and sleepiness than normal women (p<0.01). RLS score was a significant factor related to the scores for: cognitive abilities (β=-0.33; P=0.022), depression (β=0.32; P=0.001), anxiety (β=0.24; P=0.003), stress (β=0.44; P<0.001), quality of life (β=-0.23; P<0.001), insomnia (β=0.21; P=0.001), sleepiness (β=0.15; P=0.014) and PSST (β=0.28; P=0.019).

Conclusions: In the absence of health management, RLS potentially associated to depression, anxiety, sleep disruption, cognitive impairment, decreased quality of life and menstrual problem. Future intervention studies is required for support these results.

Keywords: Memory; stress; Menstruation; insomnia; dysmenorrhea
1. Introduction

Restless legs syndrome (RLS) as a sensorimotor disorder, typically known by a paresthesia and an uncontrollable urge to move the extremities, especially the legs — with symptoms that worsen at rest or during the night—which is 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).

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 the 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 profound detrimental effect on sleep; many of 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 mood, which have been related to cognitive decline (12, 13). However, the results of the few studies about cognitive performance are conflicting (14, 15). These evidence indicates that RLS patients are possibly more prone to neuropsychological complication.

On the other hands, 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 child bearing 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 which women experience one week before onset of menstruation. PD is characterized by painful cyclic cramps in the lower abdomen happening with menstruation without organic pathology(18).

RLS symptoms fluctuate with changing of estrogens in women. Within the menstrual cycle, estrogen concentrations vary significantly and aggravation of RLS symptoms within the menstrual period was reported in 29% of RLS cases (19, 20). Goecke et al. 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 had a higher prevalence of RLS versus those without it. During menstruation, the release of prostaglandins by the endometrium and elevation in the amount and intensity of contractions in the uterus leading to hypoxia and ischemia in the uterine muscles, consequently menstrual-associated pain. This increment in prostaglandin concentrations is may implicate in 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 are accumulating evidences supported the strong association between menstrual-associated pain and neuropsychological complications such as depression, aggression as well as 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).

Concurrent occurrence of psychological disorders related to PMS or menstrual problem possibly increases the adverse consequences of RLS and can be deleterious for the female’s physical and mental health.
The connection between RLS and psychopathological state and menstrual-corresponding problems in young woman has not been comprehensively investigated previously. On the other hands, the menstrual associated complications is usually considered as physiological pain and ignored by women. Regarding the 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; we aimed to evaluate the association between the mood disorders, menstrual bleeding patterns and associated manifestations with RLS among apparent healthy young women.

2. Methods

This cross-sectional survey was conducted on young women living in Birjand city, Khorasan Province, Iran in December 2019 to January 2020 (27). The sample size needed to achieve 80% power and α′ = 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 to these assumptions at least 110 participants was essential. The inclusion criteria were young female, aged between 18-24 years, having a normal menstrual cycle, being single (unmarried) and who provided 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 randomly selected based on 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%) meet the inclusion criteria and accepted to participate, making a final sample size of 118. The Ethical Committee of Birjand university of Medical Sciences confirmed the study (Code:IR.BUMS.REC.1398.160).

2.1. General information

Demographic details of participants were collected by face-to-face interview. Anthropometric parameters i.e. weight, height, waist and hip circumference were measured through excellent validated instruments and standard protocol.

2.2. RLS status

The clinical diagnosis of RLS was based on four parts of the diagnostic criteria of RLS recommended by the National Institutes of Health (29). Moreover, symptom severity 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 ranged from 0 to 40. Due to the small sample size, subjects were categorized as severe/very severe (scores of >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 have been confirmed by several studies; for instance, in study of Habibzade and co-workers the content validity was estimated by ten experts and the reliability of the tool was accepted (32).

2.3. Menstrual pattern and associated symptoms

Standard questionnaires were used to assess features of menstruation, that included: menarcheal age, menstrual pattern (regularity of menstrual cycle, cycle length and average days of bleeding), most common menstruation-associated physical symptoms and presence of PMS and/or PD (33). A diagnosis of PD was based on these criteria: pain initiating within first hours of menstruation, low abdomen pain related with the beginning of menarche and lengthen for 8-72 hour. 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 which was developed at 2003 for as a screening of PMS cases (35). The PSST includes 19 items which each question is rated on a 4-point scale scored from 0 to 3 (“none”, “mild”, “moderate” and “severe”) obtaining a total score range from 0 to 57. This instrument was validated with reliability, internal consistency, and the validity of 0.9, 0.8, and 0.7, respectively for Iranian population (36).

2.4. Neuropsychological assessment

2.4.1. Anxiety, depression and stress

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 of 21 items on a 4-point Likert scale (score: 0 to 3) subdivided on 3 subsections of 7 questions, corresponding to depression, anxiety and stress. The final score of each subsections should to be doubled. The valid and reliable Persian version of this questionnaire was used in this study (Cronbach's alpha was confirmed 0.7, 0.66 and 0.76 for depression, anxiety, and stress, respectively) (37).

2.4.2. Cognitive performance

The Cognitive Abilities Questionnaire (CAQ) captures composite dimension of cognitive performances. The CAQ includes 30 questions with total scores from 30 to 150 based on a 5-point Likert scale (1–5). Higher scores showed better cognition functions (38). The CAQ ask 7 domain including memory, inhibitory control and selective attention, decision making, planning, sustained attention, social cognition and cognitive flexibility. The validity of questionnaire and internal consistency (the Cronbach α=0.83) and good test-retest reliability (r=0.86) have been reported for Iranian subjects (38).

2.4.3. Sleep pattern

Daytime sleepiness: Excessive daytime somnolence was evaluated the Epworth Sleepiness Scale (ESS). This is a validated and reliable questionnaire including 8 items that explore about the probability of dozing in 8 different conditions. Snoozing likelihood ratings range from 0 (No) to 3 (high probability). Only 5 minutes is required to complete the ESS. Possible scores vary from 0 to 24, with higher scores indicating more odds of daytime sleepiness (39).

Insomnia status: Insomnia is described by a subjective feeling of short, unsatisfying sleep in spite of the capability to sleep falling. 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 by using a 5-point Likert scale ranged from ‘0’ (absence) to ‘4’ (very much). The calculation of total score was based on summing the seven questions, for a possible total score varying from 0 to 28. The ISI was validated in 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.

2.4.4. Quality of life (QoL)

The physical and mental aspect of QoL was explored using a 12-item Short Form Health Survey (SF-12) which had 12 items encompass different eight 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 (41).

2.5. Statistical analysis

Statistical analyses were done using the SPSS for Windows version 16.0. A Kolmogorov-Smirnov test was recruited to assess whether the data was normally distributed. All of evaluated variables that were normally distributed were analyzed by using parametric tests. For statistical analysis, participants were classified in four groups concerning to the degree of RLS. Continuous variables demonstrated as mean ± SD and compare between four groups by using One-way ANOVA and post hoc Tukey’s test. Categorical variables showed as number (percent) and compare between four categories by Chi-square test. Correlation between variables was explored using Spearman 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.

3. Results

118 subjects with a mean age of 20.6±1.7 years were included in the study. 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 WHR between different categories of RLS among study population (P>0.05; Table 1).

3.1. The Association between menstrual-associated factors with RLS severity

The features of the menstrual cycle (menstrual age, cycle length, duration of flow), PSST score, presence of PD as well as menstrual associated symptoms, in relation to presence and severity of RLS are reported in Table 2. The duration of the menstruation cycle was significantly different between the group without RLS compared to the mild RLS group (p=0.020). Also, in the severe/very severe RLS group, the mean pain intensity of PSST was less versus 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).

3.2. The relationship between neuropsychological tests with RLS severity

The normal subjects scored more favorably than those with severe/very severe RLS, on most of the cognitive ability questionnaires (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 (Table 3; p=0.52).
Correlation analysis indicated that RLS score were positively related to score of depression, anxiety, stress, insomnia, sleepiness and PSST. An inverse association was found between RLS score and cognitive abilities and QoL. These findings are shown in Tables 4.

Univariate and multivariate linear regression analysis was undertaken to investigate the relationship of RLS score and score of PSST and neuropsychological performance tests (Table 5). This revealed that RLS score were significant factors in the multivariate model associated with cognitive abilities, depression, anxiety, stress, QoL, insomnia, sleepiness and PSST scores (P<0.05).

4. Discussion
We investigated association between neuropsychological test results and menstrual pattern with RLS severity in a cross-sectional survey. There were two important findings:
Women with RLS had neuropsychological dysfunction in the domains of memory, inhibitory control and selective attention, decision making, sustain attention, depression, anxiety, stress, insomnia and daytime sleepiness compared to representative values. Furthermore, women with RLS suffered more from menstrual problem and severe PMS symptom. 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 a most frequent nervous system sensory dyskinesia disorder and an important cause of disability. We found that increasing severity of RLS was related with increasing scores for depression, anxiety, stress, insomnia, and sleepiness. Castillo et al found that the frequency of depression, aggression, and stress was nearly three times more in RLS subjects compared to the general population (28). Untreated RLS subjects presented increased psychological distress in the areas of somatization and compulsivity than matched controls (42). On the other hand, it has been shown that the cases with both depression and RLS had a greater vulnerability to develop insomnia (43).

Sleep disturbance was another problem observed among subjects with RLS. RLS may be an etiological factor, or just accompanied with other sleep complications; insomnia and decrement of sleep quality could cause daytime snoozing and psychological distress. In several pathologic conditions, the presence of RLS also aggravates mood disorders. RLS patients endure more degree of disability, fatigue and sleep disorders i.e. high sleep latency, decreased sleep duration and poorer sleep efficiency in multiple sclerosis (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 elevated quality of sleep than subjects with RLS in hemodialysis patients (46-48).

The connection between RLS symptoms and depression or anxiety is not entirely attributed to disturbed sleep; sleep-independent mechanisms possibly involve in this association too. Insomnia is a casual factor for depression and stress, and RLS lead 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 in absence of 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 aspect of QoL. The lower QoL found in women suffered from RLS in the current study is inconsistent with previous researches (45, 50-52). In a populations-based study in the United States, SF-36
instrument was used for evaluation the burden of RLS on QoL. Each of SF-36 measures in RLS person was remarkably lower than general population norms (52). RLS affect social lives and emotional and neuropsychological health of individuals (50). Happe and colleagues also reported that anxiety and depression significantly contributed in 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 partially cognitive deficits. The RLS persons showed lower ability in the Trail Making Test or category verbal fluency test than healthy controls (54). In patients with Parkinson’s disease, RLS individual had significantly worse cognitive function versus controls (55).

This is the first study investigating menstrual pattern and associated characteristics with RLS. RLS subjects have significantly lower duration of the menstruation cycle and higher PSST score. 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 hormonal factors, specially connection to the elevation of estrogen values within late pregnancy (20, 57).

Although, during pregnancy, the relation of hormonal alterations aggravate RLS is unclear, because estrogen concentrations decrease prior to 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 donor (59, 60). On the other hand, psychological comorbid to RLS is also connected to altered changes in pain thresholds and potentially predict future pain (61, 62). We speculated that mood disorders, a common complication in RLS, are also a risk factor for PMS pain severity.

The cross-sectional nature of current survey prevents any inferences concerning causality in RLS, psychological distress and menstrual-associated problems. We relied mainly on scores from the RLS questionnaire instead of 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 report their symptoms; however SF-12, DASS-21, ISI and ESS are reliable and valid instrument for measurement of these symptoms. Additional proper instruments should be applied in future researches to evaluate cognitive performance in relation to RLS. In clinical setting, our findings may broadened 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.

5. Conclusion
This study is the first to highlight the possibility that RLS may be related with psychological problems and menstrual-associated complaints. In the absence of mitigating interventions, a consequence of RLS is depression, anxiety, increased insomnia and daytime snoozing, cognitive impairment, decreased QoL and menstrual problem. Treatment of RLS has the promise to upgrade clinical outcomes which would affect one’s participation in daily functions.

Acknowledgments
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Conflict of interest The authors declare that they have no conflict of interest.
References:


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<th>Variables</th>
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<th></th>
<th></th>
<th></th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>No  (n=35)</td>
<td>Mild (n=38)</td>
<td>Moderate (n=33)</td>
<td>Severe/very severe (n=12)</td>
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<tr>
<td></td>
<td>20.88±1.30</td>
<td>20.67±1.63</td>
<td>20.69±1.64</td>
<td>21.83±2.12</td>
<td>1.75</td>
<td>0.160</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.52±2.34</td>
<td>21.26±3.72</td>
<td>20.46±2.20</td>
<td>20.11±3.95</td>
<td>1.15</td>
<td>0.330</td>
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<td>WHR</td>
<td>0.73±0.03</td>
<td>0.75±0.04</td>
<td>0.73±0.03</td>
<td>0.72±0.04</td>
<td>2.30</td>
<td>0.081</td>
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Values are presented as mean ± SD. One-way ANOVA and post hoc Tukey’s test was performed. BMI: body mass index; RLS: restless legs syndrome; WHR: waist: hip ratio.
<table>
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<tr>
<th>Variables</th>
<th>No (n=35)</th>
<th>Mild (n=38)</th>
<th>Moderate (n=33)</th>
<th>Severe/very severe (n=12)</th>
<th>Test results</th>
<th>P value</th>
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<tr>
<td>Age at menarche (y)</td>
<td>13.34±1.21</td>
<td>13.05±1.54</td>
<td>13.27±1.46</td>
<td>13.25±0.86</td>
<td>F=0.29</td>
<td>0.831</td>
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<td>Average duration of bleeding (d)</td>
<td>6.51±1.31</td>
<td>6.78±1.03</td>
<td>6.63±1.38</td>
<td>6.58±1.16</td>
<td>F=0.29</td>
<td>0.829</td>
</tr>
<tr>
<td>Duration of the menstruation cycle (d)</td>
<td>30.01±6.12</td>
<td>26.53±4.91</td>
<td>28.47±3.32</td>
<td>28.23±3.26</td>
<td>F=3.39</td>
<td>0.020*</td>
</tr>
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<td>PSST score</td>
<td>19.51±2.17</td>
<td>22.36±10.24</td>
<td>23.06±9.91</td>
<td>29.50±18.63</td>
<td>F=3.24</td>
<td>0.025*</td>
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<td>Dysmenorrhea, yes</td>
<td>24(68.6)</td>
<td>26(68.4)</td>
<td>24(72.7)</td>
<td>10(83.3)</td>
<td>X²=1.75</td>
<td>0.643</td>
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<td>Menstruation-associated physical symptoms, n(%)</td>
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<tr>
<td>Tender breasts</td>
<td>18(51.4)</td>
<td>23(60.5)</td>
<td>12(36.4)</td>
<td>5(41.7)</td>
<td>X²=4.46</td>
<td>0.215</td>
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<tr>
<td>Backache</td>
<td>24(68.6)</td>
<td>32(82.2)</td>
<td>29(87.9)</td>
<td>11(91.7)</td>
<td>X²=5.74</td>
<td>0.125</td>
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<tr>
<td>feeling of bloating</td>
<td>30(85.7)</td>
<td>35(92.1)</td>
<td>26(78.8)</td>
<td>10(83.3)</td>
<td>X²=2.59</td>
<td>0.457</td>
</tr>
<tr>
<td>Weight gain</td>
<td>17(48.6)</td>
<td>16(42.1)</td>
<td>9(27.3)</td>
<td>4(33.3)</td>
<td>X²=3.35</td>
<td>0.312</td>
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<td>Swelling of the limbs</td>
<td>12(34.3)</td>
<td>10(26.3)</td>
<td>11(33.3)</td>
<td>6(50.0)</td>
<td>X²=2.36</td>
<td>0.501</td>
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<td>joint or muscle pain</td>
<td>22(62.9)</td>
<td>25(65.8)</td>
<td>23(69.7)</td>
<td>10(83.3)</td>
<td>X²=1.84</td>
<td>0.606</td>
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<td>Gastrointestinal symptoms</td>
<td>22(62.9)</td>
<td>23(60.5)</td>
<td>20(60.6)</td>
<td>10(83.3)</td>
<td>X²=2.30</td>
<td>0.511</td>
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Data presented as mean±SD or number (%). PSST (Premenstrual Syndrome Screening Tool).
*By using One-way ANOVA and post hoc Tukey’s test or chi-square test as appropriate.
* Significance between No RLS group and Mild group
\( ^{\circ} \) Significance between No RLS group and Severe/very severe group
Table 3. Association between neuropsychological function and restless legs syndrome (RLS)

<table>
<thead>
<tr>
<th>Variables</th>
<th>RLS</th>
<th>F</th>
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<td></td>
<td>No (n=35)</td>
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<td>Test of cognitive abilities</td>
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<tr>
<td>Memory</td>
<td>26.62±2.83</td>
<td>26.87±2.70</td>
<td>26.12±3.15</td>
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<tr>
<td>Inhibitory control and selective attention</td>
<td>22.53±3.91</td>
<td>23.38±3.86</td>
<td>22.72±3.64</td>
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<td>Decision making</td>
<td>20.25±3.48</td>
<td>20.31±3.75</td>
<td>18.93±3.36</td>
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<td>Planning</td>
<td>11.62±2.67</td>
<td>11.52±2.25</td>
<td>11.52±2.48</td>
</tr>
<tr>
<td>Sustain attention</td>
<td>10.01±2.28</td>
<td>10.30±2.4</td>
<td>9.73±2.49</td>
</tr>
<tr>
<td>Social cognition</td>
<td>10.21±2.08</td>
<td>10.54±2.36</td>
<td>10.81±2.68</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>14.65±2.53</td>
<td>15.13±3.16</td>
<td>15.18±2.50</td>
</tr>
<tr>
<td>Total cognitive ability task</td>
<td>115.10±12.54</td>
<td>117.7±14.2</td>
<td>115.01±11.89</td>
</tr>
<tr>
<td>Dass-21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>8.45±8.13</td>
<td>8.69±8.2</td>
<td>10.43±9.21</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.73±6.58</td>
<td>6.52±5.27</td>
<td>8.53±7.75</td>
</tr>
<tr>
<td>Stress</td>
<td>11.85±8.12</td>
<td>14.22±9.09</td>
<td>17.76±8.94</td>
</tr>
<tr>
<td>Quality of life (SF-12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health</td>
<td>16.84±1.92</td>
<td>16.38±1.89</td>
<td>15.72±2.13</td>
</tr>
<tr>
<td>Mental health</td>
<td>18.20±3.27</td>
<td>17.83±3.27</td>
<td>16.18±3.19</td>
</tr>
<tr>
<td>SF-12 score</td>
<td>35.13±4.69</td>
<td>34.10±4.37</td>
<td>31.81±4.58</td>
</tr>
<tr>
<td>Test of sleep pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia score (ISI)</td>
<td>1.88±3.57</td>
<td>4.18±5.26</td>
<td>5.2±5.97</td>
</tr>
<tr>
<td>Daytime sleepiness score (ESS)</td>
<td>1.93±4.23</td>
<td>4.86±5.53</td>
<td>6.1±5.82</td>
</tr>
<tr>
<td>Nocturnal sleep hours</td>
<td>8.43±1.07</td>
<td>7.98±1.55</td>
<td>8.2±1.64</td>
</tr>
</tbody>
</table>

Data presented as mean±SD

*By using One-Way ANOVA. Significance of bold values are P<0.05.

<sup>a</sup> Significance between No RLS group and Severe/very severe group
<sup>b</sup> Significance between Mild RLS group and Severe/very severe group
<sup>γ</sup> Significance between Moderate RLS group and Severe/very severe group
<sup>δ</sup> Significance between No RLS group and Moderate group.
Table 4. Correlation matrix between RLS score and neuropsychological tests

<table>
<thead>
<tr>
<th>Variables</th>
<th>RLS score</th>
<th>Cognitive abilities</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
<th>Quality of life</th>
<th>Insomnia</th>
<th>Daytime sleepiness</th>
<th>PSST score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>r</td>
<td>r</td>
</tr>
<tr>
<td>Cognitive abilities</td>
<td>-0.25</td>
<td><strong>0.006</strong></td>
<td>0.33</td>
<td><strong>&lt;0.001</strong></td>
<td>0.29</td>
<td>0.001</td>
<td>0.45</td>
<td><strong>&lt;0.001</strong></td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
<td></td>
<td>0.43</td>
<td><strong>&lt;0.001</strong></td>
<td>0.45</td>
<td>0.64</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Depression</td>
<td>0.33</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td>0.29</td>
<td><strong>&lt;0.001</strong></td>
<td>0.45</td>
<td>0.64</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.29</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td>0.001</td>
<td><strong>&lt;0.001</strong></td>
<td>0.43</td>
<td>0.64</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Stress</td>
<td>-0.43</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td>-0.57</td>
<td><strong>&lt;0.001</strong></td>
<td>-0.57</td>
<td>-0.42</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Quality of life</td>
<td>-0.43</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td>-0.57</td>
<td><strong>&lt;0.001</strong></td>
<td>-0.57</td>
<td>-0.42</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.34</td>
<td>0.004</td>
<td>0.45</td>
<td>0.015</td>
<td>0.045</td>
<td>0.001</td>
<td>0.045</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>0.008</td>
<td>0.009</td>
<td>0.320</td>
<td>0.047</td>
<td>0.003</td>
<td>0.045</td>
<td>0.045</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>PSST score</td>
<td>0.27</td>
<td>-0.42</td>
<td>0.50</td>
<td>0.43</td>
<td>0.49</td>
<td>-0.42</td>
<td>0.26</td>
<td>0.24</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Note: All p-values are significant at the 0.05 level.*
Table 5. Univariate and multivariate linear regression analysis for the effect of restless legs syndrome (RLS) score on cognitive abilities, depression, anxiety, stress, quality of life, insomnia, daytime sleepiness and PSST scores as the dependent variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B(SE)</td>
<td>t</td>
<td>P value</td>
<td>B(SE)</td>
<td>t</td>
<td>P value</td>
</tr>
<tr>
<td>Cognitive abilities</td>
<td>-0.40(0.15)</td>
<td>-2.18</td>
<td>0.006</td>
<td>-0.33(0.14)</td>
<td>-1.40</td>
<td>0.022</td>
</tr>
<tr>
<td>Depression</td>
<td>0.36(0.09)</td>
<td>3.34</td>
<td>&lt;0.001</td>
<td>0.32(0.09)</td>
<td>2.83</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.25(0.07)</td>
<td>2.62</td>
<td>0.001</td>
<td>0.24(0.07)</td>
<td>2.10</td>
<td>0.003</td>
</tr>
<tr>
<td>Stress</td>
<td>0.49(0.09)</td>
<td>3.55</td>
<td>0.001</td>
<td>0.44(0.09)</td>
<td>2.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td>-0.24(0.05)</td>
<td>-5.12</td>
<td>0.001</td>
<td>-0.23(0.05)</td>
<td>-4.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.22(0.06)</td>
<td>4.10</td>
<td>0.001</td>
<td>0.21(0.06)</td>
<td>3.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>0.18(0.06)</td>
<td>3.13</td>
<td>0.008</td>
<td>0.18(0.06)</td>
<td>2.97</td>
<td>0.014</td>
</tr>
<tr>
<td>PSST</td>
<td>0.36(0.10)</td>
<td>3.21</td>
<td>0.003</td>
<td>0.28(0.10)</td>
<td>2.94</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Multivariate analysis adjusted for age and BMI.