Mood Symptoms and Restless Legs Syndrome Without Periodic Limb Movements During Sleep: Is it a Clinical Subtype?

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Frequently co-occurring restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) are postulated to share common pathophysiology. The authors compared clinical characteristics and polysomnography (PSG) parameters among 155 idiopathic, untreated RLS patients who were stratified into three groups based on periodic limb movement index (PLMI). The authors found that RLS patients without PLMS (PLMI <5) had higher depression and anxiety scores, a lower total arousal index, longer latency to REM, and a higher spontaneous arousal frequency on PSG than RLS patients with PLMS. RLS severity was associated with PLMI in RLS patients with PLMS but not without PLMS. RLS without PLMS seems to be a phenotypically distinct clinical subtype of RLS. Future study should examine whether RLS without PLMS has a different clinical course, treatment response, and pathophysiology than RLS with PLMS.

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Restless legs syndrome (RLS) is a common neurosensory motor disorder characterized by an irresistible urge to move one's body, most commonly the legs, usually with uncomfortable sensations that worsen at rest and at night.[1] Periodic limb movements during sleep (PLMS), formerly sleep myoclonus,[2] consist of brief involuntary movements of the foot and legs during sleep, often associated with sleep disruption. Clinically, RLS and PLMS frequently co-occur,[3–5] and a potential etiologic association between them has been frequently attributed to these conditions because both RLS and PLMS reliably respond to dopamine agonist treatment.[6–8] In fact, many practitioners assume that the frequency of individual movements throughout the night, commonly quantified in the Periodic Limb Movement Index (PLMI), correlates to the severity of RLS symptoms. Several pivotal trials previously have utilized reduction in polysomnography-measured PLMI as a proxy for objective clinical outcome.[9,10]

However, clinical association between severity of RLS and PLMS remains controversial. For example, Aksu et al. [11] and Garcia-Borreguero et al. [12] reported that PLMI is associated with severity of RLS symptoms. In contrast, a larger sampled study by Hornyak et al. [13] found no correlation between RLS severity and either PLMS-arousal index or PLMI among two groups: untreated RLS outpatients at a sleep disorders center and participants of the Pergolide European Australian RLS study. Furthermore, while the presence of PLMS is highly prevalent among RLS patients, a substantial minority of RLS patients (up to 20%) reportedly do not have PLMS.[5,8]

As far as we know, there has been only one study that directly compared clinical and sleep study characteristics between RLS patients with PLMS and those without PLMS. Baumann et al.[15] conducted a chart review study that compared clinical characteristics of 103 RLS patients with PLMS with 14 RLS patients without PLMS and found that RLS patients without PLMS were significantly younger, had a poorer response to dopaminergic therapy, and had a higher rate of psychiatric comorbidities than RLS patients with PLMS. However, their findings were difficult to generalize because of the small sample size (N=14) of the RLS patients without PLMS, inclusion of treated RLS patients whose PLMI was affected by RLS therapy, and lack of standardized psychiatric assessment.

Therefore, based on a large clinical database of untreated RLS patients, we selected and stratified untreated, idiopathic RLS patients into three groups on the basis of the presence and severity of PLMS and examined whether severity of PLMS was associated with RLS symptom severity and RLS-related quality of life. Furthermore, based on the previous study by Baumann et al., we hypothesized that RLS subjects without PLMS would have higher depression and anxiety ratings on standardized measures than RLS subjects with PLMS. By comparing polysomnography (PSG) and clinical

characteristics among RLS patients with and without PLMS, we aimed to determine whether there are distinct clinical features that make subtyping RLS without PLMS clinically significant.

METHODS

Subjects

This study was approved by the institutional review board of a regional university medical center in Daegu, South Korea. The target population consisted of 288 consecutive patients who were referred for evaluation of RLS at a tertiary sleep center and consented to collection of their clinical data for research purposes between August 2009 and May 2012. RLS evaluation included a full physical and neurological examination by an RLS clinical expert (YW Cho), overnight polysomnography, and serological testing to exclude potential mimics and identify secondary causes of RLS symptoms (e.g., pregnancy, neuropathy, iron deficiency, renal disease). The diagnosis of RLS was made based upon the International RLS Study Group (IRLSSG) diagnostic criteria.[16] We excluded nonadults (age <18; N=5) and those with RLS mimics and secondary causes of RLS (N=74). Additionally, 54 subjects who had comorbid sleep disorders (i.e., obstructive sleep apnea; RDI ≥5: N=48; REM sleep behavior disorder: N=6) were excluded in order to avoid confounding by a comorbid sleep disorder. Our final analytic sample consisted of 155 untreated, idiopathic RLS patients.

To be consistent with a previous study on the prevalence of PLMS in RLS,[17] we defined PLMS as having a PLMS index (PLMI; number of PLMs per hour of sleep) >5. Also, we chose to use PLMI ≤5 as the cutoff in order to create a "no PLMS" sample group that was as homogeneous as possible. Furthermore, these categories were also chosen on the basis of their close approximation of tertiles of the study sample. Based on presence and severity of PLMS, each subject was assigned to one of the following three groups: 1) subjects with PLMI ≤5 (no PLMS group; N=64), 2) subjects with 5< PLMI <30 (mild PLMS group; N=52), and 3) subjects with PLMI ≥30 (moderate-to-severe PLMS group; N=39). Figure 1 displays the study flow diagram.

Measures

Polysomnographic and PLMS recording. A full-night PSG was performed using a 32-channel Grass-Telefactor Comet digital recording system. Sleep was staged, and PLMS was scored based on the 2007 rules from the American Academy of Sleep Medicine.[18] Arousal was scored if there was an 8–12 Hz alpha rhythm for at least 3 seconds in occipital or central electroencephalographic derivations. Individual limb movements were scored if 1) the electromyographic (EMG) signal was increased by 8uV from baseline EMG and 2) the duration of the limb movement was at least 0.5 seconds and no more than 10 seconds. Movements were considered periodic if there were at least four consecutive movements with intermovement intervals no less than 5 seconds and no more than 90 seconds. The total number of PLMs per hour of sleep was quantified to yield the PLMI. PLMs were also scored with arousals, and the total number of PLMs with arousal was divided by the hours of sleep to yield the periodic limb movements arousal index.

Assessment of RLS. Each participant rated the severity of RLS symptoms based on the IRLSSG RLS Rating Scale-Korean version (IRLS-K).[19] This 10-item scale measures the impact of the symptoms on daily life, sleep, and mood. In order to assess the impact of RLS symptoms on quality of life, we also utilized the Korean version of the RLS Quality of Life Instrument (RLS Qol-K).[19] The RLS Qol-K is an 18-item scale that measures four factors (daily function, social function, sleep quality, and emotional well-being) related to quality of life in RLS.

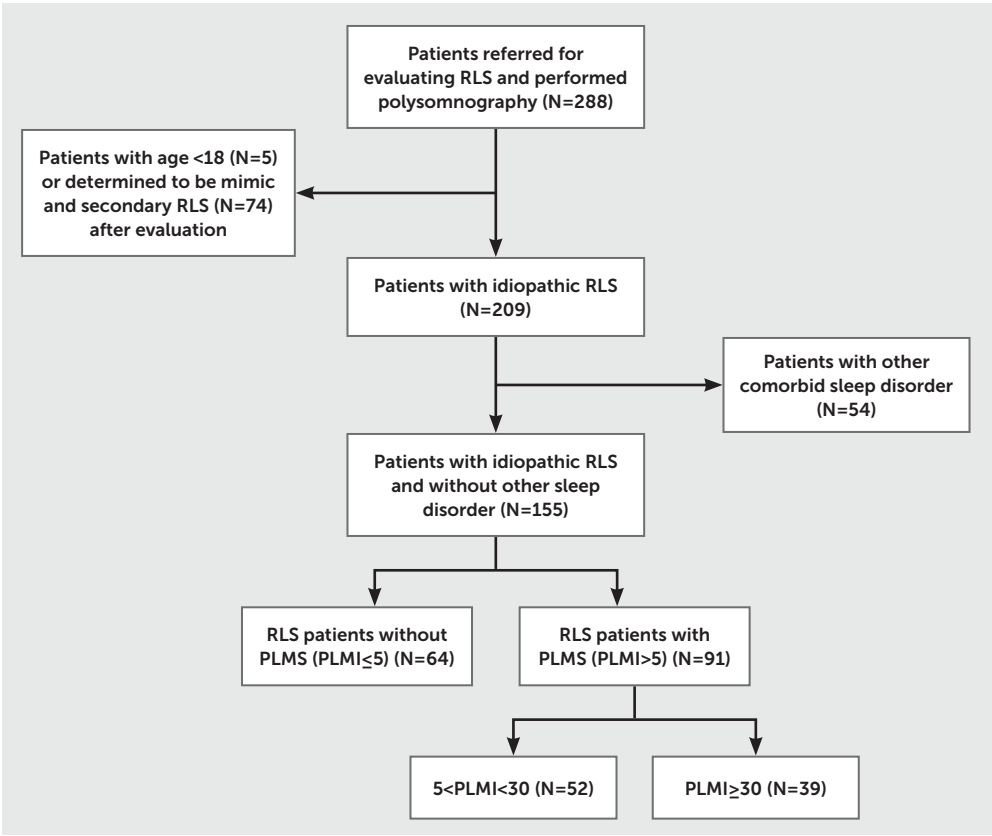
Subjective sleep measures and quality of life. The Insomnia Severity Index (ISI-K)[20] is a brief, seven-item questionnaire that measures a patient's perception of his or her insomnia. The Pittsburgh Sleep Quality Index (PSQI-K)[21] is a scale that measures the quality and patterns of sleep in seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The Epworth Sleepiness Scale (ESS-K),[22] an eight-item self-questionnaire, was used to assess the level of daytime sleepiness among the study subjects. Overall quality of life for each subject was assessed based on the 36-item Short-Form Health Survey (SF-36).[23] The SF-36 is a common measure of health-related quality of life that is often used to determine the cost-effectiveness of a health treatment.

Mental health measures. Specific assessments of depression and anxiety were based on the Korean versions of the Hospital Anxiety and Depression Scale (HADS-K) and the Beck Depression Inventory-2 (K-BDI-2).[24] The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale that consists of two seven-item subscales for anxiety (HADS-A) and depression (HADS-D).[25] Based on a systematic review of 747 studies, Bjelland et al.[26] recommended a cutoff point of 8/21 for anxiety or depression. The Beck Depression Inventory-2 (BDI-2) measures the severity of depressive symptoms and consists of 21 items that are each scored on a scale with a value of 0–3. A score of 20 and above on the BDI is generally used to identify moderate to severe clinical depression.[27] BDI-2 also consists of somatic factors and cognitive-affective factors, from which five items (items 20, 15, 19, 18, and 16) were loaded on the somatic factor, and the remaining 16 items were loaded on the cognitive-affective factor.[27,28]

Statistical Analysis

Data analysis was performed using the SPSS version 18.0, and $p<0.05$ was considered statistically significant. We compared the three groups with respect to demographic

FIGURE 1. Flow Chart of the Study



(age and gender), health-related (body mass index and medical conditions), and RLS-related (family history of RLS, mean age at onset, and duration of RLS symptoms) characteristics, based on chi-square testing for categorical variables, analysis of variance testing for continuous variables, and Scheffe testing for post-hoc testing. Clinical measures (IRLS-K, RLSQol-K, ISI, PSQI-K, ESS-K, HADS, K-BDI-2, SF-36) and PSG-derived sleep parameters between the three groups were analyzed based on multivariate analyses of covariance after adjusting for age and gender, and pair-wise comparisons were used for observing group differences. In addition, we performed multiple linear regression to further examine the association between PLMI (dependent variable) and IRLS-K (independent variable), while adjusting for age and gender.

RESULTS

Comparison of Sociodemographic Variables, Clinical Characteristics, and Quality of Life

Mean age of participants in the no PLMS group was significantly younger than that in the mild and the moderate-to-severe PLMS groups (49.7±14.5 vs. 54.4±9.4 vs. 55.7±8.9 years; p=0.02). The mean age at onset for RLS symptoms was also significantly less for the no PLMS group than the two PLMS groups (40.9±15.3 vs. 44.0±11.9 vs. 48.7±9.2 years, respectively; p=0.01). The moderate-to-severe PLMS group consisted of a lower percentage of women (53.8% vs. 82.7% vs. 73.4%; p=0.01) than the other two groups. For a detailed summary of these comparison results, see Table 1.

Across the three groups, no differences were found in medical conditions and other clinical characteristics, including family history of RLS, duration of RLS symptoms, ferritin level, IRLS-K score, and RLS Qol-K score. SF-36 scores, including all subscale scores, were also similar across the three groups. Similarly, no difference in subjective quality of sleep and daytime sleepiness, measured by ISI-K, PSQI-K, and ESS-K, was found across the three groups.

In a bivariate linear regression model with PLMI as the dependent variable and IRLS-K as the independent variable, no significant association (β=–0.631, p=0.256) was found between PLMI and RLS symptom severity when we analyzed all the subjects together. Similarly, adjusting for age and gender in the multiple regression model showed no association between PLMI and RLS severity (β=–0.458, p=0.405). However, when we excluded the no PLMS group and reanalyzed the subsample of mild and moderate-to-severe PLMS groups with increasing thresholds (PLMI >5, >15, and >30), association between RLS severity and PLMI became stronger and statistically significant among subjects with PLMI >15 (Table 2).

Comparison of Mental Health-Related Variables

Depression and anxiety symptoms were generally higher in the no PLMS group than in the two PLMS groups. The mean HADS-K score was generally higher (18.5±7.5 vs. 15.9±7.3 vs. 15.7±7.0; p=0.12) in the no PLMS group, although this did not reach statistical significance after correction for multiple testing; in particular, the anxiety subscale scores of HADS-K were significantly elevated in the no PLMS group in comparison to the two PLMS groups (9.1±4.4 vs. 7.3±3.8 vs. 7.1±4.2; p=0.03; not corrected for multiple testing). Also, the proportion of those who were screened to have significant depression (defined as a HADS-K score of 8 or above) was significantly higher in the no PLMS group than in the two PLMS groups (65.1% vs. 46.0% vs. 41.0%; p=0.03). The mean K-BDI-2 score (19.7±9.8 vs. 15.6±10.5 vs. 16.5±9.6; p=0.03)

TABLE 1. Comparison of Sociodemographic and Clinical Variables, Subjective Sleep Measures, and Quality of Life[a]

Characteristic	A) PLMI <5 (N=64)	B) 5≤ PLMI <30 (N=52)	C) PLMI ≥30 (N=39)	F/χ^2	p	Scheffe
Demographic variables						
Age (years)	49.7±14.5	54.4±9.4	55.7±8.9	4.0	0.02	a<c
Gender (% female)	47 (73.4%)	43 (82.7%)	21 (53.8%)	9.3	0.01	
Health variables						
Body mass index	22.6±3.1	23.3±2.2	22.5±4.6	0.8	0.44	
Medical diseases						
Musculoskeletal disease	8 (12.5%)	6 (11.5%)	3 (7.7%)	17.7	0.06	
Heart disease	0	0	4 (10.3%)			
Hypertension	5(7.8%)	4 (7.7%)	4 (10.3%)			
Diabetes	1(1.6%)	2 (3.8%)	3 (7.7%)			
Cancer	0	0	2 (5.1%)			
Others	14 (21.9%)	14 (26.9%)	8 (20.5%)			
Clinical characteristics						
Family history of RLS (% with history)	15 (23.4%)	9 (17.3%)	6 (15.4%)	1.21	0.544	
Mean age at onset	40.9±15.3	44.0±11.9	48.7±9.2	4.5	0.01	a<c
Duration of symptom (years)	8.8±8.7	10.3±10.0	7.0±7.4	1.6	0.21	
Ferritin (ng/mL)	68.9±67.7	49.5±35.3	61.6±59.2	1.6	0.20	
IRLS-K	28.8±6.2	27.3±6.6	27.5±7.4	1.3	0.29	
RLS Qol-K	32.1±7.3	31.3±9.5	31.4±10.7	0.1	0.91	
Subjective sleep measures						
ISI-K	15.9±5.5	16.4±6.3	16.7±6.5	0.0	0.97	
PSQI-K	11.2±4.2	12.2±3.5	12.1±4.7	0.6	0.54	
ESS-K	7.3±4.3	7.7±4.7	7.03±4.6	0.5	0.60	
SF–36						
PF	62.9±25.7	62.7±23.7	63.6±26.4	0.1	0.94	
RP	48.7±43.3	45.5±42.5	65.0±41.7	1.9	0.16	
BP	36.0±22.4	44.6±28.4	45.6±28.3	1.7	0.20	
GH	42.5±24.3	40.9±21.7	43.5±20.9	0.1	0.89	
VT	44.3±18.8	47.4±21.4	50.7±19.5	0.3	0.48	
SF	62.9±25.9	63.9±28.4	66.3±26.1	0.1	0.94	
RE	50.2±44.1	62.1±44.7	71.4±44.4	1.7	0.19	
MH	55.5±18.2	64.6±20.9	59.3±20.3	2.0	0.13	
PCS	46.7±18.5	48.1±22.1	53.6±19.0	0.9	0.39	
MCS	51.4±19.7	55.7±23.5	58.3±18.9	0.6	0.56	
SF–36 total	50.7±19.3	54.0±22.8	58.2±19.2	0.8	0.44	

[a] Adjusted age and gender as covariates for IRLS-K, RLS Qol-K, ISI-K, PSQI-K, and ESS-K, and SF–36; multivariate analyses of covariance were used for analysis. IRLS-K, Korean version of International Restless Legs Syndrome Severity Scale; RLS Qol-K, Korean version of RLS Quality of Life Questionnaire; ISI-K, Korean version of Insomnia Severity Index; PLMI, Periodic Limb Movement Index; PSQI-K, Korean version of Pittsburgh Sleep Quality Index; ESS-K, Korean version of Epworth Sleepiness Scale; SF-36, 36-item Short-Form Health Survey; PF, physical functioning; RP, role physical; BP, body pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotion; MH, mental health; RH, reported health; PCS, physical component summary; MCS, mental component summary.

and the proportion of clinical depression (defined as a BDI score of 20 or above; 49.2% vs. 24.0% vs. 30.8%; p=0.02) were significantly higher in the no PLMS group than the other two PLMS groups. However, no significant difference was found among the three groups in terms of somatic domain and cognitive-affective domain scores of the K-BDI-2. Of note, none of the participants were being treated for depression or anxiety. For a detailed summary of these comparison results, see Table 3.

Comparisons of PSG-Derived Sleep Parameters

As expected, PLMI (0.4±1.1 vs. 14.8±7.5 vs. 84.4±60.6; p<0.001) and PLM-arousal index (0.03±0.1 vs. 2.6±3.0 vs. 11.0±20.3; p<0.001) were the lowest in the no PLMS group.

TABLE 2. Multiple Regression Analysis With the Periodic Limb Movement Index (PLMI) as the Dependent Variable and the International Restless Legs Scale (IRLS) as the Independent Variable (Adjusted for Age and Gender)

	Unadjusted Models				Adjusted Models[a]			
Group	B	SE	p-value	R^2	B	SE	p	R^2
For all subjects (N=155)	0.631	0.554	0.256	0.002	0.458	0.548	0.405	0.037
For subjects with PLMI >5 only (N=91)	1.509	0.787	0.059	0.041	1.437	0.773	0.059	0.067
For RLS subjects with PLMI >15 only (N=65)	1.984	0.963	0.044	0.067	1.996	0.966	0.043	0.097
For RLS subjects with PLMI >30 only (N=39)	3.095	1.238	0.017	0.145	3.076	1.268	0.020	0.152

[a] Multiple regression models with age, gender, and IRLS as covariates.

TABLE 3. Comparison of Depression and Anxiety Measures Among Three Groups of Restless Legs Syndrome Subjects[a]

Measure	A) PLMI <5 (N=64)	B) 5≤ PLMI <30 (N=52)	C) PLMI ≥30 (N=39)	F/χ^2	p	Pairwise
HADS-K total	18.5±7.5	15.9±7.3	15.7±7.0	2.2	0.12	
HADS-K-D subscale	9.4±4.2	8.6±4.2	8.7±3.8	0.6	0.57[b]	
HADS-K-A subscale	9.1±4.4	7.3±3.8	7.1±4.2	3.6	0.03[b]	
HADS-K-D score >8 (%)	41 (65.1%)	23 (46.0%)	16 (41.0%)	6.9	0.03[b]	
HADS-K-A score >8 (%)	44 (69.8%)	31 (62.0%)	24 (61.5%)	1.1	0.59[b]	
K-BDI-2 total	19.7±9.8	15.6±10.5	16.5±9.6	3.5	0.03	a>c
Cognitive-affective domain	6.5±5.1	4.3±5.8	5.7±4.5	2.1	0.13[b]	
Somatic domain	13.0±5.7	11.6±6.5	11.8±5.8	1.0	0.36[b]	
K-BDI-2 score >20 (%)	31 (49.2%)	12 (24.0%)	12 (30.8%)	8.3	0.02	

[a] Adjusted age and gender as covariates for HADS-K, HADS-K-D, HADS-K-A, K-BDI-2; multivariate analyses of covariance were used for analysis. Chi-square methods were used for analyzing HADS-K-A scores 8 and above, HADS-K-D scores 8 and above, K-BDI-2 <20, K-BDI-2 ≥20, and cells. HADS-K: Korean version of Hospital Anxiety and Depressive scale; K-BDI-2: Korean version of Beck Depression Inventory-2; PLMI, Periodic Limb Movement Index.
[b] After Bonferroni correction (α=0.025; p=0.05/2 comparisons), p<0.025 for HADS-K and K-BDI-2 subscales.

The lowest mean spontaneous arousal index (5.2±4.4 vs. 6.9±3.8 vs. 8.1±6.8; p=0.01) was observed in the moderate-to-severe PLMS group, while the total arousal index (18.4±20.8 vs. 10.7±5.4 vs. 8.6±5.0; p=0.002) was higher in the moderate-to-severe PLMS group versus the two other groups. Notably, the mean duration of latency to REM was significantly longer (122.9±63.2 vs. 105.5±65.6 vs. 88.0±64.7 minutes; p=0.03) in the no PLMS group than in the other groups. Otherwise, there was no significant difference between the groups in terms of total sleep time, sleep-onset latency, or sleep efficiency. For a detailed summary of these comparison results, see Table 4.

DISCUSSION

In our study sample of idiopathic RLS patients, we found that presence of PLMS is not associated with subjective sleep quality, RLS severity, and quality of life. We also found that PLMI is associated with RLS severity only in RLS patients with more severe PLMS (PLMI >15). Furthermore, lack of PLMS appears to be associated with significantly higher depression and anxiety among RLS patients, and RLS patients without PLMS had distinct PSG parameters such as lower total arousal index, longer latency to REM, and a higher spontaneous arousal frequency than RLS patients with PLMS.

Interestingly, in our study, the proportion of those without PLMS (PLMI <5) was 41%, which is higher than previously reported.[5] Unlike many previous studies, we carefully selected for idiopathic untreated RLS patients (N=155) by excluding a large number of patients with secondary causes of RLS (N=74) and those with comorbid sleep disorders (e.g., obstructive sleep apnea [RDI ≥5]: N=48), in whom PLMS is very common.[29,30] In a large community-based, multiethnic epidemiologic study, PLMS was reported to be less prevalent in Chinese Americans compared with Caucasian, Hispanic, or African Americans.[31] By extension, East Asians with RLS may have lower prevalence of PLMS than Caucasians with RLS. Also, in our study, subjects in both the mild and moderate-to-severe PLMS groups were significantly older and more likely to be male than RLS patients in the no PLMS group. This is consistent with previous reports of higher prevalence of PLMS among the elderly[32,33] and in men.[11,34,35] Nevertheless, the high prevalence of RLS without PLMS in our carefully characterized clinical sample questions the presumed etiologic linkage between RLS and PLMS for a substantial portion of RLS patients and strongly

TABLE 4. Comparison of Polysomnography Data[a]

Item	A) PLMI <5 (N=64)	B) 5≤ PLMI ≤30 (N=52)	C) PLMI >30 (N=39)	F	p	Pairwise
Total in bed (minutes)	442.2±30.5	449.7±32.8	422.4±65.0	2.7	0.07	
Total sleep time (minutes)	321.1±100.9	327.1±83.9	279.6±131.7	1.1	0.34	
Sleep-onset latency (minutes)	25.8±30.4	25.8±33.5	35.5±64.4	0.3	0.71	
REM latency (minutes)	122.9±63.2	105.5±65.6	88.0±64.7	3.8	0.03	a>c
Wake after sleep onset (minutes)	95.2±79.0	88.2±86.1	107.3±76.9	0.6	0.57	
Sleep efficiency (%)	72.1±21.0	72.4±16.7	63.9±27.4	0.8	0.47	
N1 (% total sleep time)	14.7±13.0	14.0±6.4	19.3±17.6	0.9	0.42	
N2 (% total sleep time)	46.0±10.9	42.5±10.7	44.5±14.8	0.8	0.45	
N3 (% total sleep time)	22.0±10.3	23.8±9.3	19.4±11.5	0.6	0.53	
REM (% total sleep time)	18.5±7.7	19.8±7.1	16.5±9.5	1.2	0.29	
PLMI	0.4±1.1	14.8±7.5	84.4±60.6	86.9	<0.001	a<b<c
PLM arousal index	0.03±0.1	2.6±3.0	11.0±20.3	11.32	<0.001	a<c, b<c
Arousal index-spontaneous	8.1±6.8	6.9±3.8	5.2±4.4	5.1	0.01	a>c
Arousal index-total	8.6±5.0	10.7±5.4	18.44±20.8	6.5	0.002	a<c, b<c

[a] Adjusted age and gender as covariates; multivariate analyses of covariance were used for analysis. PLMI, Periodic Limb Movement Index.

suggests an independent pathophysiology for this subgroup of RLS patients.

Subjective sleep measures (PSQI-K, ISI-K, and ESS-K) seemed to be similar across the three groups when stratified based on PLMI. In other words, presence of PLMS in RLS does not seem to have much clinical impact on subjective sleep-related symptoms. However, we found a significant correlation between PLMI and severity of RLS only in RLS subjects with PLMI >15. Previously, there have been conflicting reports about the correlation between severity of RLS and PLMI among RLS patients,[11–13] and inclusion of RLS subjects without PLMS in previous studies might have led to inconsistent results. Also, our findings suggest potentially overlapping etiologic association between RLS and PLM only among RLS patients with more severe PLMS, but not among RLS patients without PLMS. Clinically subtyping RLS without PLMS and analyzing the RLS subjects separately based on presence of PLMS might lead to more consistent, replicable findings in future studies on etiopathogenesis of RLS.

Another distinct finding was the high prevalence—nearly two-thirds (65.1%) based on HADS-K and almost half of the group (49.2%) based on K-BDI-2—of clinically significant depression in the no PLMS group. Our findings are consistent with a previous report by Baumann et al. that restless legs symptoms without PLMS seem to have higher rates of psychiatric comorbidities than RLS patients with PLMS.[36] Depression and anxiety have been previously noted to be common among RLS patients in the community and in specialty clinics.[37–39] Our study indicates that this subgroup of RLS patients without PLMS seems to be disproportionately at risk for clinical depression. This warrants careful evaluation of mood symptoms, as the presence of depression has a greater negative impact on health-related quality of life than sleep disturbance or duration of RLS.[40] This finding is especially pertinent for RLS patients in South Korea, where mental disorder and psychiatric treatment remain highly stigmatized. Despite high levels of depression and anxiety, none of the participants in our study were receiving psychiatric treatment or under the care of a psychiatrist.

A recently published study also reported that RLS patients who complain of painful sensations had more severe anxiety and depressive symptoms but had lower PLMI than patients without painful RLS.[41] Unfortunately, we do not know whether painful RLS—asthenia crurum dolorosa—was more common in the no PLMS group than in the other two PLMS groups. Future study should closely examine whether PLMS status has any bearing on the pain-depression relationship in RLS. Perhaps the original description of RLS by Karl-Axel Ekbom in 1945, which describes two types of RLS, asthenia crurum paresthetica and asthenia crurum dolorosa, might have implications on etiopathophysiology of RLS.[42]

Furthermore, there were several differences in objective sleep measures among the three groups. Notably, the no PLMS group had significantly longer latency to REM sleep, higher spontaneous arousal index, and lower total arousal index compared with the two PLMS groups. Investigation of REM latency in depression and anxiety has a long history. Shortened REM latency in depression[43] and, to a lesser degree, delayed REM latency for anxiety[44,45] have been reported and studied as potential biological markers for these states. Previously, Brand et al.[46] compared latency to REM between RLS patients with and without depressive symptoms and found no difference, but the same study reported that REM latency in RLS patients was significantly longer than in major depressive disorder patients without RLS. Hornyak et al.[47] also reported that RLS patients had longer latency to REM compared with normal controls. In our study, despite high prevalence of clinical depression, the no PLMS group had the longest latency to REM sleep. From these results, we can make an inference that, unlike idiopathic depression, depression in RLS is not associated with REM latency, while degree of PLMS is associated with REM latency in RLS.

Predictably, the no PLMS group had a significantly lower PLM arousal index and total arousal index compared with the two PLMS groups. Alternatively, the no PLMS group had a significantly higher spontaneous arousal index than either of the two PLMS groups. Increased sleep fragmentation and arousals have been previously reported among depressed patients, and sleep continuity disturbances are concomitant, prodromal, and residual symptoms of major depression that subside on depression remission.[48,49] In our study, higher levels of depression in the no PLMS group may have led to an increased spontaneous arousal index in the no PLMS group, and future study should investigate whether improved sleep continuity results in amelioration of either depression or RLS symptoms among RLS patients without PLMS. A recent analysis by Szentkiralyi et al. based on two prospective cohort studies reported that clinically relevant depressive symptoms (CRDS) might be a risk factor for RLS, and the same study found that RLS at baseline, to a lesser degree, was also an independent risk factor of incident CRDS. Findings were similar in another longitudinal study of the Nurses' Health Study cohort by Li et al., suggesting a bidirectional relationship between depression and RLS.[50,51] In order to elucidate the potentially overlapping biological mechanism underlying the association between depression and RLS, further studies should be carried out to examine and compare the pathophysiological characteristics between RLS with and without PLMS.

A major strength of our study is that it is the first study to compare clinical and PSG characteristics in a carefully characterized group of clinical RLS patients with and without PLMS, based on previously validated instruments and standardized PSG methods. Limitations of our study include the cross-sectional study design, which makes it difficult to draw conclusions about direction of causality among the variables. We employed single overnight PSG, which does not account for night to night PLMS variability within an individual. Also, we did not assess the qualitative aspects of the sensory symptoms (e.g., pain) of RLS patients that might have influenced their mental health ratings.

In summary, RLS without PLMS is associated with high levels of anxiety and depression and has several distinct PSG characteristics. Bauman et al. reported that patients with restless legs symptoms without PLMS tend to be treatment-resistant to dopaminergic therapy.[36] In the future, clinical outcomes of patients with RLS without PLMS should be compared with patients with RLS with PLMS to see whether absence of PLMS is a predictor of treatment response for a specific RLS or depression therapy. Along with distinct clinical and PSG characteristics, differential response to treatment in RLS without PLMS could pave a way toward future research to identify divergent biological pathways underlying etiopathogenesis of RLS without PLMS versus with PLMS.

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