https://doi.org/10.5664/jcsm.9230

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

The prevalence and clinical characteristics of restless legs syndrome in patients with iron deficiency anemia in Korea

Hyoeun Bae, MD[1]; Keun Tae Kim, MD[1]; Mi Hwa Heo, MD[2]; Young-Rok Do, MD[2]; Yong Won Cho, MD, PhD[1]

[1]Department of Neurology, Keimyung University School of Medicine, Daegu, Korea; [2]Division of Hematology-Oncology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

Study Objectives: While the prevalence and clinical characteristics of restless legs syndrome (RLS) are known to vary according to ethnicity, a detailed evaluation of this condition among patients with iron deficiency anemia (IDA) has not yet been reported in an Asian population. We investigated the prevalence and clinical characteristics of RLS in patients with IDA in Korea compared with age- and sex-matched patients diagnosed with idiopathic RLS.

Methods: This prospective single-center study was performed at a regional university hospital. Consecutive patients with IDA were enrolled over a 4-year period. Clinical interviews and laboratory tests were conducted at the first visit. RLS diagnosis was confirmed through face-to-face interviews. We randomly selected patients with idiopathic RLS without comorbid medical disorders from our sleep center dataset as control patients. The clinical characteristics of both groups were compared.

Results: We enrolled 124 patients with IDA. Fifty (40.3%) patients were diagnosed with RLS, with 82% exhibiting severe to very severe symptoms. Patients with IDA and RLS were older and reported more sleep deterioration than patients with IDA without RLS. Patients with IDA and RLS also had a more depressed mood and higher periodic limb movement index scores than patients with idiopathic RLS.

Conclusions: The prevalence of RLS among patients with IDA in Korea was high, with the majority having severe to very severe symptoms. Patients with IDA and RLS had poorer sleep quality and more emotional problems than patients with IDA without RLS. Therefore, patients with IDA should be screened for RLS to prevent adverse effects on the quality of sleep and life.

Keywords: restless legs syndrome, iron deficiency, anemia, sleep

Citation: Bae H, Kim KT, Heo MH, Do Y-R, Cho YW. The prevalence and clinical characteristics of restless legs syndrome in patients with iron deficiency anemia in Korea. *J Clin Sleep Med*. 2021;17(7):1447–1452.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The prevalence and severity of restless legs syndrome (RLS) is higher in patients with iron deficiency anemia (IDA) than in the general population, and the clinical characteristics of RLS differ according to ethnicity. However, detailed evaluations of patients with IDA have not yet been reported in Korea.

Study Impact: The study revealed that patients with IDA and RLS show poorer sleep quality and more emotional problems than those with IDA without RLS. The periodic limb movement index scores were higher in patients with IDA and RLS than in those with idiopathic RLS. Thus, screening for RLS should be performed for patients with IDA.

INTRODUCTION

Restless legs syndrome (RLS) is a chronic sensorimotor neurological disorder characterized by leg discomfort and an urge to move the legs. The associated symptoms have a diurnal variation, and often have an adverse effect on sleep since they are exacerbated at night. The disease burden can range from mild discomfort to a severe disturbance that reduces nightly sleep durations to less than 6 hours, thus significantly impairing the quality of sleep and life.[1,2] Iron deficiency in the brain plays a fundamental role in RLS pathogenesis. Iron deficiency anemia (IDA), chronic kidney disease, and pregnancy are the most common causes of secondary RLS, all of which involve iron deficiency in the brain. RLS prevalence increases with the progression of these diseases, and iron supplementation has been found to reduce the symptoms of RLS.[3]

Both the prevalence and severity of RLS are higher in patients with IDA compared with the general population. Previous studies have reported the prevalence of RLS to be 5%–10% in the general population[4–7] and 25%–43% in patients with IDA.[8–11] The correlation between RLS severity and serum ferritin level has been well defined.[3,12,13] Iron deficiency in the brain may lead to dysfunction of the striatal dopamine neurotransmission pathway, resulting in RLS.[12,14] Therefore, it is believed that appropriate iron supplementation would be able to relieve symptoms and improve sleep and the quality of life in patients with RLS.

The prevalence and clinical characteristics of RLS have been found to vary depending on genetics, race, and geographical region. The prevalence of RLS has been reported to be higher in Western (5%–12%) compared with Asian (1%–8%) populations.[15] Furthermore, subtle discrepancies in terms

of genetics and clinical characteristics have also been observed.[16–18] To our knowledge, a detailed evaluation of the clinical characteristics of RLS associated with IDA has not yet been reported in an Asian population. This study aimed to investigate and compare the clinical characteristics of RLS in patients with IDA in Korea and make comparisons with age- and sex-matched patients diagnosed with idiopathic RLS (iRLS).

METHODS

Study design and participants

This prospective single-center study enrolled consecutive patients (aged > 19 years) with IDA at a regional university hospital in Korea from January 2016 to December 2019. Clinical interviews and laboratory tests were conducted at the first visit in the hemato-oncology or neurology department outpatient clinic. The diagnosis of IDA was based on the following criteria: (1) serum ferritin < 20 ng/mL and (2) hemoglobin < 14 g/dL (< 12 g/dL in women). RLS diagnosis was confirmed through face-to-face interviews conducted by an RLS expert (Y.W.C.); all 5 consensus 2012 International Restless Legs Syndrome Study Group criteria were satisfied.[19] The exclusion criteria comprised the following: diseases similar to RLS (eg, muscle spasm, anxiety disorder, varicose vein, and peripheral neuropathy), chronic diseases (eg, systemic lupus erythematous, rheumatic arthritis, diabetic neuropathy, HIV, amyloidosis, alcoholism, chronic kidney disease, acute bleeding, or uncontrolled bleeding; IDA-related cancer), pregnancy, cognitive impairment, comorbid sleep disorders (with the exception of insomnia), previous treatment for RLS, and inability to complete the questionnaire. To compare patients with IDA and RLS (IDA+RLS) with patients with iRLS, we selected 50 age- and sex-matched patients diagnosed with iRLS. The comparison groups were randomly selected from our sleep center database.

The study was approved by the institutional ethics committee of the regional hospital. Written informed consent was obtained from all participants.

Procedures

Demographic and clinical information were collected, and blood tests were conducted to determine iron profiles. The validated Korean versions of the following questionnaires were also administered: Insomnia Severity Index,[20] Pittsburgh Sleep Quality Index,[21] Beck Depression Inventory,[22] Beck Anxiety Inventory,[23] and Short Form–36 health survey (SF-36).[24] In addition, the International Restless Legs Syndrome Study Group Severity Scale was used to assess RLS severity.[25,26] Overnight polysomnography (PSG) was performed, if required, using a digital polygraph system (Natus Medical Incorporated, Grass-Telefactor twin, version 2.6, West Warwick, RI) according to standard protocols.

Statistical analysis

Continuous variables are presented as number (%) or mean ± standard deviation. Continuous data were compared using the Mann-Whitney *U* test or *t* test. Categorical data were analyzed with the chi-square test, Fisher exact test, and 1-way analysis of variance. Analysis of covariance was performed with age correction. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY). The level of statistical significance was set at $P < .05$.

RESULTS

IDA population

The study population consisted of 124 patients with IDA. The detailed demographic and clinical profiles of the patients are shown in **Table 1.** The average duration of IDA was 3.14 ± 2.01 years, and 18 (14.5%) patients were receiving iron supplementation at the time of enrollment. The cause of IDA in the majority of patients was unknown; gastric ulcer with bleeding and hypermenorrhea were cited as causes in 44 (35.5%) and 26 (20.9%) of patients, respectively. Taken together, the latter 2 conditions were the cause of IDA in over 50% of the patients (**Table 1**).

Comparisons of laboratory and clinical parameters in patients with IDA+RLS vs IDA without RLS

RLS was diagnosed in 50 (40.3%) patients. The symptom severity in patients with IDA+RLS was distributed as follows: mild (0%), moderate (14%), severe (40%), and very severe (42%). Thus, 33.1% of the patients with IDA had severe to very severe RLS (RLS sufferers). The average age of the IDA+RLS group (54.02 ± 12.50 years) was older than that of the IDA without RLS (IDA−RLS) group (47.22 ± 12.35 years). Hemoglobin levels were higher in the IDA+RLS group, while no statistically significant differences in iron parameters (iron, ferritin, total iron binding capacity, and transferrin saturation) were observed (**Table 2**). The durations and treatment of IDA were not significantly different between groups. Both groups showed a female predominance (IDA+RLS, 45 [90.0%]; IDA−RLS, 64 [86.5%]). Patients with IDA+RLS had poorer sleep-related parameters than patients with IDA−RLS. Patients with IDA+RLS reported increased sleep latency, sleep disturbance, use of sleeping medications, and daytime dysfunction; sleep duration and habitual sleep efficiency were also reduced. Overall sleep quality (total Pittsburgh Sleep Quality Index score) was significantly lower in the IDA+RLS group compared with the IDA−RLS group (IDA+RLS group, 13.02 ± 3.78; IDA−RLS, 6.00 ± 3.24). In terms of emotional and health problems accompanied by poor sleep quality, the IDA+RLS group exhibited a greater level of depression (as determined via the Beck Depression Inventory), with an overall reduction in both physical and mental health, compared with the IDA−RLS group (**Table 2**).

Comparisons of laboratory and clinical parameters between patients with IDA+RLS vs those with iRLS

Demographic characteristics did not significantly differ between the IDA+RLS group and the iRLS group. The average ages of the iRLS and IDA+RLS groups were 51.98 ± 9.34 years and 54.02 ± 12.50 years, respectively. There was a female predominance in both groups (iRLS group, 44 [88.0%]; IDA+RLS group, 45 [90.0%]). The IDA+RLS group exhibited a

Table 1—Demographic and clinical characteristics of the study population.

	IDA (n = 124)
Age, y	49.96 ± 12.81
Sex, female, n (%)	109 (87.9)
BMI, kg/m^2	23.24 ± 3.64
Previous illness, yes, n (%)	58 (48.7)
Current medications, yes, n (%)	54 (45.4)
Hemoglobin, g/dL	9.34 ± 1.70
Iron, μg/dL	29.93 ± 31.62
TIBC, μg/dL	419.24 ± 60.83
TSAT, %	7.41 ± 7.87
Ferritin, ng/mL	10.29 ± 23.84
IDA duration, y	3.14 ± 2.01
IDA treatment, yes, n (%)	18 (14.5)
IDA cause, n (%)	
Gastric ulcer with bleeding	44 (35.5)
Hypermenorrhea	26 (20.9)
Stomach cancer operation	4 (3.2)
Diffuse large B-cell lymphoma	2 (1.6)
Unknown	48 (38.7)

BMI = body mass index, IDA = iron deficiency anemia, TIBC = total iron-binding capacity, TSAT = transferrin saturation.

lower iron profile than the iRLS group (**Table 2**). There were no significant differences in International Restless Legs Syndrome Study Group Severity Scale or 36-Item Short Form Survey scores between the 2 groups. The distributions of symptom severity, as based on the International Restless Legs Syndrome Study Group Severity Scale, were also not significantly different. Patients in the IDA+RLS group reported a shorter RLS duration and more depressed mood than patients in the iRLS group; no differences were observed for insomnia and quality of sleep.

PSG was performed in 26 patients with IDA+RLS and 40 patients with iRLS (**Table 3**). The periodic limb movement (PLM) score was higher in the IDA+RLS group (38.77 ± 55.34) than in the iRLS group (9.55 ± 17.76). There was no statistically significant difference in age or sex between the patients who underwent PSG and those who did not in either the IDA+RLS or iRLS groups. No differences in other sleep parameters were observed between the 2 groups.

DISCUSSION

This study documented a high prevalence (40.3%) of RLS among patients with IDA in Korea, which was similar to rates reported in the United States (31%)[27] and Europe (25%–43%).[10,11] In the IDA group, 33.1% of the patients had severe to very severe RLS and were therefore classified as RLS sufferers; this proportion was slightly higher than that reported in a population consisting of Western patients (23.9%).[27] A previous study among the general population in Korea reported that 3.9% fulfilled the criteria for definite RLS, while 1.48% were categorized as RLS sufferers.[28] Thus, the prevalence of RLS among patients with IDA in the present study was approximately 10 times higher than in the general population; furthermore, the majority of patients with RLS exhibited significant symptoms that required management. Similar to previous studies, hypermenorrhea and gastrointestinal bleeding were cited as the primary causes of IDA in the present study.[29]

Patient age in the IDA+RLS group was significantly greater than that in the IDA-RLS group. A previous study reported that the prevalence of RLS increases with age.[4] A study of Western patients with IDA showed an increase in RLS prevalence with age; however, this did not reach statistical significance.[27] Our results clearly show a tendency for older patients with IDA to show RLS in Korea. Age also seems to be an important factor in IDA+RLS as well as iRLS. There was a female predominance in both the IDA+RLS and IDA−RLS groups due to the higher prevalence of IDA in women.[30]

Hemoglobin levels were higher in the IDA+RLS group than in the IDA−RLS group. However, all other iron parameters, including ferritin level, were not significantly different between the 2 groups. This implies that hemoglobin level alone was not a direct relevant factor for RLS. Further studies are needed to investigate the role of iron metabolism and RLS in patients with frank anemia. There were no significant differences in the duration of IDA between the 2 groups. However, unlike treatment for patients with IDA−RLS, treatment for patients with IDA+RLS should be targeted toward RLS; this is often disregarded in the routine management of IDA in Korea. This is pertinent, as a previous study reported that the administration of oral iron only achieved a marginal response in patients with IDA+RLS.[31] Even intravenous iron supplementation, which is a more aggressive treatment, may not be sufficient in some patients with IDA+RLS; a previous study reported that the disease burden was not adequately reduced in 24% of patients following the administration of a standard IDA treatment dose consisting of a 1,000 mg intravenous infusion of low-molecular-weight iron dextran.[32] As the improvement in anemia without increments in ferritin levels would be insufficient for managing RLS in patients with IDA, a more deliberate approach is needed. Successful intravenous administration of iron for patients with IDA+RLS likely requires more than the establishment of a minimally adequate body iron store to ensure distribution to the brain.

The IDA+RLS group showed higher sleep-related comorbidity compared with the IDA−RLS group. This is supported by a previous study, which also reported poorer sleep quality among patients with IDA+RLS compared with patients with IDA−RLS.[27] Thus, these results confirm that decreased sleep and quality of life, as well as increased emotional problems, are particularly characteristic of patients with IDA+RLS. Poor sleep quality is associated with cognitive dysfunction and depression,[33] and adversely affects cardiovascular, inflammatory, and metabolic functions.[34] Thus, sleep problems place patients with IDA+RLS at a greater risk of developing sleep-related comorbidities compared with patients with IDA−RLS. Therefore, it is essential that patients with IDA are appropriately screened for RLS.

Table 2—Comparisons of demographic, laboratory, and clinical parameters between patients with IDA+RLS vs patients with IDA−RLS or iRLS.

	IDA+RLS (n = 50)	IDA−RLS (n = 74)	*P**	iRLS (n = 50)	*P*†
Age, y	54.02 ± 12.50	47.22 ± 12.35	.003	51.98 ± 9.34	.358
Sex, female, n (%)	45 (90.0)	64 (86.5)	.780‡	44 (88.0)	> .99‡
Previous illness, yes, n (%)	27 (57.4)	31 (43.1)	.125	20 (40.0)	.086
Current medication, yes, n (%)	26 (54.2)	28 (39.4)	.113	19 (41.3)	.212
Hemoglobin, g/dL	10.27 ± 1.36	8.70 ± 1.62	< .001	13.68 ± 1.01	< .001
Iron, μg/dL	33.86 ± 24.22	26.37 ± 36.96	.231	100.59 ± 31.15	< .001
TIBC, μg/dL	411.19 ± 66.32	426.54 ± 54.99	.202	328.90 ± 47.07	< .001
TSAT, %	8.61 ± 6.44	6.31 ± 8.89	.140	30.86 ± 9.87	< .001
Ferritin, ng/mL	9.53 ± 8.98	10.82 ± 30.21	.771	68.50 ± 55.91	< .001
IDA duration, y	3.28 ± 2.14	3.04 ± 1.92	.516		
IDA treatment, yes, n (%)	3 (6.0)	14 (18.9)	.060‡		
IRLSS, n (%)	27.92 ± 6.80			27.22 ± 6.79	.613
Mild (1–10)	0			2 (4.0)	.495‡
Moderate (11–20)	7 (14.0)			5 (10.0)	.549‡
Severe (21–30)	20 (40.0)			29 (58.0)	.157‡
Very severe (31–40)	21 (42.0)			14 (28.0)	.140‡
RLS QoL	57.94 ± 23.51			58.79 ± 22.47	.858
RLS duration, y	7.47 ± 9.71			14.70 ± 12.56	.003
ISI	17.24 ± 6.01	6.11 ± 5.31	< .001	15.86 ± 6.14	.260
PSQI total	13.02 ± 3.78	6.00 ± 3.24	< .001	11.92 ± 4.82	.210
BDI	17.55 ± 11.87	9.64 ± 7.62	< .001	12.92 ± 7.62	.024
BAI	15.68 ± 10.27	5.53 ± 5.64	< .001	10.6 ± 8.85	.027
SF-36 total	51.96 ± 23.11	72.37 ± 17.10	< .001	57.31 ± 20.48	.230

**P* value for IDA+RLS vs IDA−RLS. †*P* value for IDA+RLS vs iRLS. ‡Fisher exact test. Analysis of covariance: age correction. BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, IDA = iron deficiency anemia, IDA+RLS = iron deficiency anemia with restless legs syndrome, IDA−RLS = iron deficiency anemia without restless legs syndrome, iRLS = idiopathic restless legs syndrome, IRLSS = International Restless Legs Syndrome Study Group Severity Scale, ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, QoL = quality of life, RLS = restless legs syndrome, SF-36 = Short Form-36 health survey, TIBC = total iron-binding capacity, TSAT = transferrin saturation.

Table 3—Polysomnographic results of patients with IDA+RLS and iRLS.

	IDA+RLS (n = 26)	iRLS (n = 40)	*P**
TST, min	353.56 ± 125.64	367.17 ± 71.44	.904
Latency to stage N2 sleep, min	29.04 ± 43.92	22.14 ± 17.58	.362
Latency to sleep onset, min	19.58 ± 31.10	17.25 ± 14.44	.297
Latency to REM sleep, min	110.25 ± 94.74	131.33 ± 76.67	.123
Sleep efficiency %	71.63 ± 20.49	76.94 ± 13.00	.469
TST, stage N1 sleep, %	14.72 ± 9.50	32.48 ± 130.64	.145
TST, stage N2 sleep, %	50.57 ± 10.66	48.17 ± 10.63	.298
TST, stage N3 sleep, %	14.40 ± 7.33	18.11 ± 6.78	.087
TST, REM sleep, %	20.31 ± 8.83	20.70 ± 7.11	.951
AHI total, events/h	3.05 ± 4.74	1.64 ± 2.17	.548
PLM index total	38.77 ± 55.34	9.55 ± 17.76	.021
Arousal index total	16.09 ± 12.09	11.56 ± 5.46	.098

*Mann-Whitney *U* test. AHI = apnea-hypopnea index, IDA+RLS = iron deficiency anemia with restless legs syndrome, iRLS = idiopathic restless legs syndrome, PLM = periodic limb movement, REM = rapid eye movement, TST = total sleep time.

Age and sex did not differ between patients with IDA+RLS and patients with iRLS. The distribution of RLS symptom severity was also similar between the 2 groups. However, the duration of RLS symptoms was shorter among patients with IDA+RLS, which reflects the role of iron deficiency in the pathogenesis of RLS. Iron deficiency in the brain leads to the dysfunction of the dopamine neurotransmission pathway,[12,14] which, in turn, fosters the development of RLS symptoms. Indeed, serum ferritin levels and RLS severity are known to be positively correlated.[3,12,13]

Greater adverse effects on emotion and mood were observed in patients with IDA+RLS compared with patients with iRLS, while the quality of sleep was similarly reduced in both groups. Iron deficiency has been reported to increase the risk of mood disorders, including depression and anxiety.[35,36] Furthermore, RLS and sleep deterioration have been shown to have negative effects on emotion.[33,37] The combined effects of iron deficiency, RLS symptoms, and reductions in sleep quality likely accounted for the poorer emotional state observed in patients with IDA+RLS compared with patients with iRLS in the present study. Therefore, more proactive detection and management protocols for ferritin levels, RLS, and sleep disturbances are required to successfully alleviate emotional problems in patients with IDA+RLS.

The PLM index score was higher in the IDA+RLS group than in the iRLS group. A previous study also showed an association between lower ferritin levels and a higher PLM index score.[38] Therefore, it can be ascertained that lower ferritin levels have a role in the pathological mechanisms of both RLS and PLM. A higher PLM index score can lead to sleep disturbances, as well as an increased risk of cardiovascular and cerebrovascular diseases.[39,40] Thus, patients with IDA+RLS are at a greater risk of PLM-associated comorbidities than patients with iRLS, emphasizing the need for vigilant screening of RLS and appropriate treatment.

This study had several limitations. First, this was a single-center study, with a relatively small sample size. However, the number of included patients was sufficient to reveal significant differences between the IDA+RLS, IDA−RLS, and iRLS groups. Second, PSG was not conducted in some of the RLS populations in this study. Future studies should incorporate PSG assessments and use larger sample sizes across multiple centers.

Our study showed a high prevalence of RLS among patients with IDA, with the majority exhibiting severe to very severe symptoms, which were slightly higher than those reported in studies conducted in Western countries. Poorer sleep quality and emotional problems were more prevalent in patients with IDA+RLS than in patients with IDA−RLS. Furthermore, PLM index scores were higher in patients with IDA+RLS than in patients with iRLS. Therefore, it is important that patients with IDA are screened for RLS to prevent adverse effects on the quality of sleep and life. In addition, the treatment goals for patients with IDA+RLS should focus on the resolution of both anemia and RLS symptoms.

ABBREVIATIONS

IDA, iron deficiency anemia
IDA+RLS, iron deficiency anemia with restless legs syndrome
IDA−RLS, iron deficiency anemia without restless legs syndrome
iRLS, idiopathic restless legs syndrome
PLM, Periodic Limb Movement
PSG, polysomnography
RLS, restless legs syndrome

REFERENCES

1. Allen RP, Stillman P, Myers AJ. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: prevalence and characteristics. *Sleep Med*. 2010;11(1):31–37.
2. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med*. 2010;11(9):807–815.
3. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing*. 1994;23(3):200–203.
4. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;165(11): 1286–1292.
5. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med*. 2004;164(2): 196–202.
6. Ulfberg J, Nyström B, Carter N, Edling C. Restless legs syndrome among working-aged women. *Eur Neurol*. 2001;46(1):17–19.
7. Ulfberg J, Nyström B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord*. 2001;16(6):1159–1163.
8. Akyol A, Kiylioglu N, Kadikoylu G, Bolaman AZ, Ozgel N. Iron deficiency anemia and restless legs syndrome: is there an electrophysiological abnormality? *Clin Neurol Neurosurg*. 2003;106(1):23–27.
9. Aspenstroem G. Pica and restless legs in iron deficiency. Article in Swedish. *Sven Lakartidn*. 1964;61:1174–1177.
10. Ekbom KA. Restless legs syndrome. *Neurology*. 1960;10(9):868–873.
11. O'Keeffe ST. Restless legs syndrome: a review. *Arch Intern Med*. 1996;156(3): 243–248.
12. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med*. 2004;5(4):385–391.
13. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Mov Disord*. 2007;22(Suppl 18):S440–S448.
14. Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom disease). *Sleep Med*. 2014;15(11):1288–1301.
15. Koo BB. Restless leg syndrome across the globe: epidemiology of the restless legs syndrome/Willis-Ekbom disease. *Sleep Med Clin*. 2015;10(3):189–205.
16. Kim MK, Cho YW, Shin WC, et al. Association of restless legs syndrome variants in Korean patients with restless legs syndrome. *Sleep*. 2013;36(12):1787–1791.
17. Li G, Tang H, Wang C, et al. Association of BTBD9 and MAP2K5/SKOR1 with restless legs syndrome in Chinese population. *Sleep*. 2017;40(4):zsx028.
18. Zhu XY, Wu TT, Wang HM, et al. Clinical features and subtypes of restless legs syndrome in Chinese population: a study of 359 patients. *Sleep Med*. 2019;59: 15–23.
19. Allen RP, Picchietti DL, Garcia-Borreguero D, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med*. 2014;15(8):860–873.
20. Cho YW, Song ML, Morin CM. Validation of a Korean version of the Insomnia Severity Index. *J Clin Neurol*. 2014;10(3):210–215.
21. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. *Sleep Breath*. 2012;16(3):803–812.
22. Lim S-Y, Lee E-J, Jeong S-W et al. The validation study of Beck Depression Scale 2 in Korean version. *Anxiety Mood* 2011;7:48-53.

23. Yook S, Kim Z. A clinical study on the Korean version of Beck Anxiety Inventory: comparative study of patient and non-patient. *Korean J Clin Psychol*. 1997;16: 185–197.
24. Kim SH, Jo MW, Lee SI. Psychometric properties of the Korean Short Form-36 health survey version 2 for assessing the general population. *Asian Nurs Res Korean Soc Nurs Sci*. 2013;7(2):61–66.
25. Yang J-G, Kim D-H, Lee J-H, et al. The reliability and validity of the Korean versions of the international restless legs scale and the restless legs syndrome quality of life questionnaire. *J Korean Neurol Assoc*. 2010;28:263–269.
26. Walters AS, LeBrocq C, Dhar A, et al; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. 2003;4(2):121–132.
27. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am J Hematol*. 2013;88(4):261–264.
28. Cho YW, Shin WC, Yun CH, et al. Epidemiology of restless legs syndrome in Korean adults. *Sleep*. 2008;31(2):219–223.
29. DeLoughery TG. Iron deficiency anemia. *Med Clin North Am*. 2017;101: 319–332.
30. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016;387(10021):907–916.
31. Bryant BJ, Yau YY, Arceo SM, Hopkins JA, Leitman SF. Ascertainment of iron deficiency and depletion in blood donors through screening questions for pica and restless legs syndrome. *Transfusion*. 2013;53(8):1637–1644.
32. Mehmood T, Auerbach M, Earley CJ, Allen RP. Response to intravenous iron in patients with iron deficiency anemia (IDA) and restless leg syndrome (Willis-Ekbom disease). *Sleep Med*. 2014;15(12):1473–1476.
33. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med*. 2007;3(5):519–528.
34. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis*. 2009;51(4):294–302.
35. Chen MH, Su TP, Chen YS, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study. *BMC Psychiatry*. 2013;13(1):161.
36. Shafi M, Taufiq F, Mehmood H, Afsar S, Badar A. Relation between depressive disorder and iron deficiency anemia among adults reporting to a secondary healthcare facility: a hospital-based case control study. *J Coll Physicians Surg Pak*. 2018;28(6):456–459.
37. Becker PM, Sharon D. Mood disorders in restless legs syndrome (Willis-Ekbom disease). *J Clin Psychiatry*. 2014;75(7):e679–e694.
38. Li J, Moore H IV, Lin L, et al. Association of low ferritin with PLM in the Wisconsin Sleep Cohort. *Sleep Med*. 2015;16(11):1413–1418.
39. Lin TC, Zeng BY, Chen YW, et al. Cerebrovascular accident risk in a population with periodic limb movements of sleep: a preliminary meta-analysis. *Cerebrovasc Dis*. 2018;46(1-2):1–9.
40. Somers VK, White DP, Amin R, et al; American College of Cardiology Foundation. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *Circulation*. 2008;118(10):1080–1111.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 3, 2020
Submitted in final revised form March 2, 2021
Accepted for publication March 2, 2021
Address correspondence to: Yong Won Cho, MD, PhD, Department of Neurology, Keimyung University School of Medicine, 1035, Dalgubeol-daero, Dalseo-gu, Daegu, 42601, South Korea; Tel: +82-53-258-7832; Email: neurocho@gmail.com

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. This work was performed at Keimyung University Dongsan Medical Center. The authors report no conflicts of interest.