



Involvement of legs and other body parts in patients with restless legs syndrome and its variants

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ABSTRACT

Background: Restless legs syndrome (RLS) is characterized by the urge to move the legs accompanied by movement-responsive, abnormal sensations, which worsen at rest and night. We investigated the distribution of sensory symptoms and clinical correlations in patients with RLS and its variants.

Methods: Eighty-nine patients diagnosed with RLS or RLS variants (age 61.4 ± 18.5 years 40 M/49 F) according to established criteria, with the exclusion of those with augmentation, were included in this study. The international RLS rating scale (IRLS) was used to assess the severity of RLS/RLS variant symptoms.

Results: Eighty-three patients (93.3%) had RLS, and 6 patients (6.7%) had RLS variants. Among the patients with RLS and RLS variants, 33 patients (36.0%) reported restlessness involving other body parts: arms (16.9%) were the most frequent region, followed by the back (10.1%), abdomen (6.7%), and buttocks (4.5%). There were no between-group differences in clinical characteristics, except for the level of sleep disturbances being higher in patients with RLS variants ($n=6$) than in patients with RLS ($n=83$). No significant difference was observed in clinical characteristics including RLS severity and treatment between patients with RLS only ($n=57$) and patients with RLS with other body part involvement ($n=26$). No relationship was observed between the onset of symptoms in the legs and other body parts, but the IRLS scores for legs and other body parts were significantly correlated.

Conclusion: We should recognize that RLS can involve not only legs but also other body parts to varying degrees in each patient.

1. Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a sleep-related movement disorder, characterized by the urge to move the legs accompanied by movement-responsive, abnormal sensations, which worsen at rest and night [1]. In accordance with its name, the abnormal sensations predominantly involve the legs, but in some RLS patients, other body parts such as the face [2] and arms [3,4] can also be affected [1]. Previous studies have reported that 34.6–57% of RLS patients showed additional upper limb involvement [3–5], but the prevalence of restlessness in other body regions is unclear.

Augmentation, known to be a side effect of long-term treatment with dopaminergic medications, causes an expansion of symptoms from the legs to other body parts [6]. Therefore, augmentation should be ruled out when RLS symptoms expand to other body parts in association with a 2–4 h time advance of symptom onset.

Although rare, RLS variants, in which the symptoms predominantly or solely occur in body parts other than the legs, such as restless face [7], abdomen [8] and lower back [9], have been reported. We have reported a rare case of a “restless bladder” in which unpleasant sensations in the lower abdomen and perineum were relieved by urination [10]. However, the prevalence of RLS variants has never been studied

Abbreviations: RLS, restless legs syndrome; WED, Willis-Ekbom disease; IRLS, International RLS rating scale; ESS, Epworth sleepiness scale; PSQI, Pittsburgh Sleep Quality Index; BDI-II, Beck depression inventory

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in clinical settings or the general population. Additionally, no study has focused on the prevalence and impact of restlessness in body parts other than legs (face, arm, chest, back, abdomen and perineum) in RLS patients. We performed a cross-sectional study to investigate the distribution and frequency of restlessness symptoms in different parts of the body and their clinical correlations in patients with RLS and its variants.

2. Methods

Between April 2016 and April 2018, 93 consecutive patients with RLS or RLS variants (41 M/52 F; age, 61.5 ± 18.7 years) were initially recruited from the outpatient clinic of the Department of Neurology and Center of Sleep Medicine, Dokkyo Medical University. Four patients with augmentation due to dopaminergic treatment, diagnosed according to the International RLS study group criteria proposed by Allen et al. [11], were excluded, given the possible effects on the distribution of symptoms in the body parts. Finally 89 patients with RLS or RLS variants (age 61.4 ± 18.5 years; 40 M/49 F) were included in this study.

All participants completed questionnaires regarding their habits (smoking and caffeine and alcohol intake). Information about disease duration and family history of RLS, restlessness of the legs and other body parts, and the use of drug treatments such as dopaminergic drugs and alpha-2-delta ligands was obtained.

RLS was diagnosed via face-to-face interview when patients fulfilled the following 4 essential features after excluding RLS mimics, such as polyneuropathy, leg edema, arthritis and leg cramps, by clinical examination: 1) an urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs; 2) the urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity; 3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement; and 4) the urge to move the legs and any accompanying unpleasant sensations only occur or are worse in the evening or night than during the day [1]. A diagnosis of RLS variants was made when the abnormal sensations and restlessness predominantly or solely occurred in body parts other than the legs and their symptoms fulfilled the 4 essential features of RLS when applied in a modified manner to the involved body parts. The severity of restlessness in the legs and other body parts was rated with the International Restless Legs Syndrome Study Group (IRLSSG) rating scale (IRLS) [12]. Daytime sleepiness was evaluated by the Japanese version of the Epworth sleepiness scale (ESS) [13], and the subject's sleep status was assessed by the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [14]. The following 7 PSQI component scores were also evaluated (range, 0–3): C1, sleep quality; C2, sleep latency; C3, sleep duration; C4, habitual sleep efficiency; C5, sleep disturbances; C6, use of sleeping medications; and C7, daytime dysfunction. The Beck depression inventory (BDI)-II was used to evaluate depressive symptoms [15].

This study was performed in accordance with the 1964 Helsinki Declaration and was approved by the institutional review boards of Dokkyo Medical University Hospital. All subjects gave written informed consent for participation in this study.

2.1. Statistical analysis

Categorical variables between two groups were compared using the chi-square test or Fisher's exact test. The Mann-Whitney *U* test was used for the comparison of continuous variables between two groups. Correlations between IRLS for legs and other body parts with clinical parameters were assessed by using Spearman's rank correlation coefficients. The Wilcoxon signed-rank test was used to analyze the relationship between the onset age of symptoms in the legs and other body parts. Two-tailed *p* values of < 0.05 were considered statistically

Table 1
Patient characteristics.

Age (y)	61.4 ± 18.5
Sex (M/F)	40/49
Smoking, n (%)	12 (13.5)
Caffeine, n (%)	71 (79.8)
Alcohol, n (%)	47 (52.8)
RLS family history, n (%)	22 (24.7)
Disease duration (y)	
RLS	9.7 ± 10.8
Restlessness in other body parts	5.8 ± 8.9
Drug treatment for RLS, n (%)	53 (59.6)
Dopaminergic drug	46 (51.7)
Alpha-2-delta ligand	19 (21.3)
Use of anti-depressants, n (%)	9 (10.1)
Use of anti-histaminergics, n (%)	9 (10.1)
IRLS score for legs	19.6 ± 10.3
IRLS score for other body parts	19.6 ± 9.0
ESS score	6.8 ± 5.3
PSQI global score	8.7 ± 4.2
PSQI component scores	
C1, sleep quality	1.6 ± 0.8
C2, sleep latency	1.7 ± 1.1
C3, sleep duration	1.7 ± 1.1
C4, habitual sleep efficiency	0.9 ± 1.2
C5, sleep disturbances	1.1 ± 0.6
C6, use of sleeping medications	1.0 ± 1.4
C7, daytime dysfunction	0.8 ± 0.9
BDI-II	11.7 ± 7.6

RLS = restless legs syndrome; IRLS = international RLS study group rating scale; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth sleepiness scale; BDI-II = Beck depression inventory-II.

significant. IBM SPSS software V.25.0 (IBM SPSS, Tokyo, Japan) and GraphPad Prism 8 for macOS (Ver. 8.1.2; GraphPad Software, San Diego, California, USA) were used for statistical analyses and creating figures.

3. Results

The patient characteristics are presented in Table 1. Fifty-three patients (59.6%) had received drug treatment. Nine patients (10.1%) and 9 patients (10.1%) were treated with anti-depressants and anti-histaminergics, respectively. The disease duration for RLS was longer than that of restlessness in other body parts. Regarding symptom severity, the IRLS scores for legs and other body parts did not differ. Eighty-three patients (93.3%) had RLS, and 6 patients (6.7%) had RLS variants. Thirty-two patients (36.0%) reported restlessness involving other body parts: arms (16.9%) were the most frequent region, followed by the back (10.1%), abdomen (6.7%), and buttocks (4.5%) (Table 2). Among RLS patients, the frequency of restlessness involving body parts

Table 2
Distribution of restlessness symptoms among 89 patients with RLS/RLS variants.

Distribution of restlessness symptoms	Frequency
RLS, n (%)	83 (93.3)
RLS variants, n (%)	6 (6.7)
Restlessness in other body parts, n (%)	32 (36.0)
Face, n (%)	1 (1.1)
Chest, n (%)	1 (1.1)
Shoulder, n (%)	1 (1.1)
Arm, n (%)	15 (16.9)
Abdomen, n (%)	6 (6.7)
Back, n (%)	9 (10.1)
Perineum, n (%)	1 (1.1)
Bladder, n (%)	1 (1.1)
Buttocks, n (%)	4 (4.5)
Other regions, n (%)	2 (2.2)

RLS = restless legs syndrome.

Table 3
Comparison of characteristics between patients with RLS and RLS variants.

	RLS (n=83)	RLS variants (n=6)	P value
Age	62.0 ± 18.3	52.8 ± 21.2	0.26
Sex (M/F)	38/45	2/4	0.69
Smoking, n (%)	11 (13.3)	1 (16.7)	1.0
Caffeine, n (%)	67 (80.7)	4 (66.7)	0.60
Alcohol, n (%)	44 (53.0)	3 (50.0)	1.0
RLS family history, n (%)	20 (24.1)	2 (33.3)	0.63
Disease duration (y)			
Restlessness in legs	9.8 ± 10.8	3.1 ± 4.2	0.26
Restlessness in other body parts	6.2 ± 9.6	4.1 ± 5.2	0.76
Drug treatment, n (%)	49 (59.0)	4 (66.7)	1.0
Dopaminergic drug	43 (51.8)	3 (50.0)	1.0
Alpha-2-delta ligand	19 (22.9)	0 (0.0)	0.33
Use of anti-depressants, n (%)	8 (9.6)	1 (16.7)	0.48
Use of anti-histaminergics, n (%)	9 (10.8)	0 (0.0)	1.0
IRLS score for legs	19.6 ± 10.3	19.0 ± 14.1	1.0
IRLS score for other body parts	18.8 ± 9.0	22.5 ± 9.5	0.37
ESS score	6.8 ± 5.3	6.3 ± 5.4	0.90
PSQI global score	8.7 ± 4.2	8.8 ± 5.3	0.87
PSQI component scores			
C1, sleep quality	1.6 ± 0.8	1.8 ± 0.8	0.40
C2, sleep latency	1.7 ± 1.1	1.5 ± 1.4	0.67
C3, sleep duration	1.7 ± 1.0	1.2 ± 1.2	0.25
C4, habitual sleep efficiency	0.9 ± 1.2	0.7 ± 1.2	0.58
C5, sleep disturbances	1.1 ± 0.6	1.5 ± 0.5	0.045
C6, use of sleeping medications	1.0 ± 1.4	0.8 ± 1.2	0.92
C7, daytime dysfunction	0.7 ± 0.9	1.3 ± 1.2	0.19
BDI-II	11.7 ± 7.8	10.8 ± 5.3	0.90

RLS=restless legs syndrome.
IRLS=international RLS study group rating scale.
PSQI=Pittsburgh Sleep Quality Index.
ESS=Epworth sleepiness scale.
BDI-II=Beck depression inventory-II.

other than legs was 31.3%. Table 3 shows the clinical characteristics of patients with RLS (n=83) and RLS variants (n=6). There was no difference in clinical background or clinical parameters, including medication for RLS, the use of anti-depressants and anti-histaminergics, disease duration and IRLS, ESS, PSQI global and BDI-II scores. The patients with RLS variants had a higher sleep disturbance score (PSQI component score C5) than did the patients with RLS. Additionally, comparisons between patients with RLS only (n=57) and RLS with other body part involvement (n=26) revealed no differences in clinical parameters, except the latter group was younger (Table 4). The number of body parts involved (2.0 ± 0.3 vs. 2.2 ± 0.6, p=0.16) and involvements of body parts other than legs (1.1 ± 0.3 vs. 1.2 ± 0.6, p=0.32) did not significantly differ between patients with and without dopaminergic therapy.

Among those with restlessness in both legs and other body parts, 40.0% had leg symptoms followed by other body part symptoms, 6.7% had symptoms of the legs and other body parts at the same time and 53.3% had other body part symptoms followed by leg symptoms. There was no correlation between the onset age of RLS and restlessness in other body parts among the RLS patients with other body part involvement (Fig. 1). There was a significant positive correlation between IRLS scores for the legs and other body parts (r=0.67, p < .001; Fig. 2). The IRLS scores for the legs positively correlated with ESS scores (r=0.23, p=0.035) and PSQI global scores (r=0.49, p < .001), but not with BDI-II scores. In contrast, the IRLS scores for other body parts did not correlate with the ESS, global PSQI or BDI-II scores.

4. Discussion

This is the first study to assess the frequency and distribution of restlessness in body parts other than the legs and clinical correlations in patients with RLS and its variants in a cross-sectional design. The frequency of RLS variants was 6.7% in our cohort, and restlessness in other

Table 4
Comparison of characteristics between patients with RLS with and without other body part involvement.

	RLS only (n=57)	RLS with other body part involvement (n=26)	P value
Age	65.9 ± 15.6	53.5 ± 21.1	0.013
Sex (M/F)	26/31	12/14	0.96
Smoking, n (%)	10 (17.5)	1 (3.8)	0.16
Caffeine, n (%)	48 (84.2)	19 (73.1)	0.23
Alcohol, n (%)	29 (50.9)	15 (57.7)	0.56
RLS family history, n (%)	10 (17.5)	10 (38.5)	0.053
Disease duration (y)			
Restlessness in legs	9.7 ± 10.9	10.1 ± 11.0	0.91
Restlessness in other body parts	–	6.2 ± 9.6	–
Drug treatment, n (%)	32 (56.1)	17 (65.4)	0.43
Dopaminergic drug	29 (50.9)	14 (53.8)	0.80
Alpha-2-delta ligand	16 (28.1)	3 (11.5)	0.16
Use of anti-depressants, n (%)	6 (10.5)	2 (7.7)	1.0
Use of anti-histaminergics, n (%)	8 (14.0)	1 (3.8)	0.26
IRLS score for legs	18.3 ± 10.7	22.5 ± 8.8	0.15
IRLS score for other body parts	–	18.8 ± 9.0	–
ESS score	6.4 ± 5.2	7.8 ± 5.5	0.29
PSQI global score	8.6 ± 4.1	8.9 ± 4.5	0.88
PSQI component scores			
C1, sleep quality	1.5 ± 0.8	1.7 ± 0.9	0.67
C2, sleep latency	1.8 ± 1.0	1.5 ± 1.2	0.15
C3, sleep duration	1.6 ± 1.1	1.9 ± 0.9	0.18
C4, habitual sleep efficiency	0.9 ± 1.2	1.1 ± 1.2	0.33
C5, sleep disturbances	1.1 ± 0.6	1.1 ± 0.6	0.75
C6, use of sleeping medications	1.1 ± 1.4	0.9 ± 1.4	0.55
C7, daytime dysfunction	0.8 ± 0.9	0.8 ± 0.9	0.83
BDI-II	11.4 ± 8.2	12.4 ± 6.7	0.36

RLS=restless legs syndrome.
IRLS=international RLS study group rating scale.
PSQI=Pittsburgh Sleep Quality Index.
ESS=Epworth sleepiness scale.
BDI-II=Beck depression inventory-II.

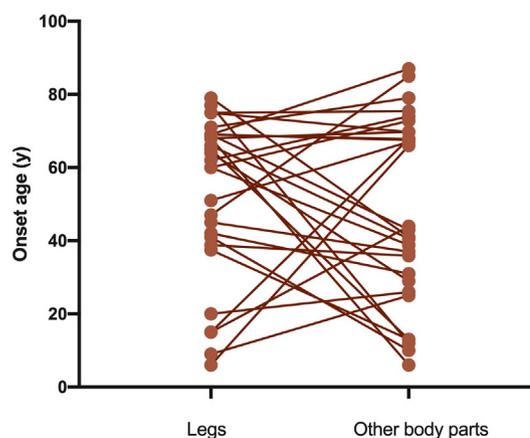


Fig. 1. Relationship between age at onset of symptoms in the legs and other body parts. p = 0.58, Wilcoxon signed-rank test.

body parts was observed in 36.0% of the patients, with arms (16.9%) being the most frequent region, followed by the back (10.1%), abdomen (6.7%), and buttocks (4.5%). As previously reported, arms constituted the most common region of restlessness in body parts other than the legs. However, restlessness in the trunk (n=16, 18.0%), such as the

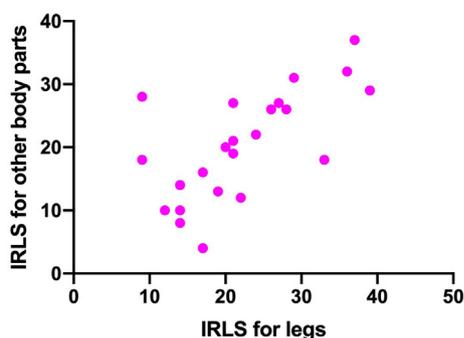


Fig. 2. Correlation between the IRLS scores for the legs and IRLS scores for other body parts.

$r = 0.67$, $p < .001$, Spearman's rank correlation coefficients.

chest, back and abdomen, was not infrequent. In the present study, involvement of the face (1.1%) and bladder (1.1%) were rarely found.

Michaud et al. [4] compared RLS patients with and without arm restlessness and found there was no difference in polysomnography findings and clinical background, except for the severity of RLS being higher in the RLS patients with arm restlessness than in those without. However, treatment for RLS or augmentation was not described. Unlike the study by Michaud et al. [4], RLS severity was not different between patients with RLS only and RLS with involvement of other body parts in our study, which excluded patients with augmentation. Karroum et al. [3] studied 44 RLS patients after excluding 12 patients with dopaminergic augmentation and found that 57% of patients had restlessness symptoms in the upper limbs. There was significant positive correlation between the percentage of the affected area in the upper limbs and that of the lower limbs; however, RLS severity was not related to the percentage of affected body surface, as in our study. Holmes et al. [16] reported that arm restlessness was found in 34% of 152 RLS patients but was not related to treatment or RLS severity. In a review on RLS variants including 12 articles, the clinical symptoms of RLS variants did not differ from those of RLS [17]. Therefore, except for augmentation, it is unlikely that restlessness in other body parts is more often seen in severe RLS patients; this agrees with the findings of our study.

In our study, restlessness in other body parts was likely milder than leg symptoms among the RLS patients. The IRLS scores for other body parts correlated with the IRLS scores for the legs but did not correlate with sleepiness, sleep status or depressive symptoms, whereas the IRLS scores for legs did correlate with sleepiness and sleep status. Milder symptoms in body parts other than the legs may lead to an underestimation of restlessness in other body parts by both patients and physicians.

We found that although there were no clinical differences between patients with RLS and RLS variants, except for sleep disturbances being more prevalent in patients with RLS variants, and between those with RLS only and RLS with other body part involvement, among those with leg and other body part involvement, the IRLS scores for the legs and other body parts were significantly correlated. This finding may suggest the concept that RLS and RLS variants belong to the same spectrum syndrome. Supporting this, in a single case report of a patient with restless arm, late emergent RLS contributed to the diagnosis of his “restless limb”, and a dopamine agonist was markedly effective [18].

Moreover, all 3 patients with restless abdomen were homozygous for the most common RLS/periodic limb movements in sleep (PLMS)-associated risk allele of the BTBD9 gene, all had PLMS on polysomnography and one of whom later developed RLS [8]. Thus, it is possible to hypothesize that restlessness syndrome involving the limb and trunk constitutes the same clinical entity. A prospective study including a large sample ($n = 1592$) of RLS patients showed that 60% of RLS patients reported the disappearance of symptoms at the 2-year follow up [19], whereas the natural course of restlessness in other body

parts or symptoms of RLS variants has not been studied.

Differences in the clinical restlessness phenotype of body part involvement may result from supraspinal hyperexcitability in different anatomical substrates (cervical, thoracic and lumbar levels); however, determinants for the involvement of different body regions remain unclear [17]. To explain the predominantly lower leg involvement in RLS, progressive caudorostral degeneration of spinal dopamine terminals was assumed [20]. However, we failed to show precedence of leg symptoms over other body part symptoms and found that restlessness in other body parts could emerge with a large variability in onset time and severity in each patient.

As limitations of this study, recall bias should be considered due to the cross sectional design, and genetic testing for RLS or PLMS was not performed. Second, a limited number of patients underwent polysomnography, and we could not use polysomnographic parameters, including PLMS, to establish correlations with clinical factors in this study. Third, the University Hospital setting may have affected the frequency and severity of RLS and restlessness in other body parts, as referrals are not necessary to visit our hospital, although there are some refractory patients who are referred to our hospital. Fourth, the RLS variant group may have been too small to detect statistical significance in differences in the clinical parameters between RLS and RLS variant groups. Fifth, among patients with restlessness in both legs and other body parts, 40.0% had leg symptoms followed by other body part symptoms. Although patients with augmentation defined as International RLS study group criteria were excluded from this study, we cannot exclude the possibility that extension to previously unaffected limbs or body parts could be initial sign of augmentation in those patients. Prospective studies with a large sample are needed to understand the natural course of restlessness in other body parts and to confirm that RLS and RLS variants lie along a continuous spectrum of WED/RLS as a restlessness syndrome potentially involving any body part.

In conclusion, even in the absence of augmentation, involvement of other body parts is not rare in patients with RLS. We should recognize that WED/RLS could involve not only legs but also other body parts to varying degrees in each patient.

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Nothing to report.

Declaration of Competing Interest

None.

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