



Research article

Restless legs syndrome variants: A systematic review

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ABSTRACT

Introduction: Restless Legs Syndrome (RLS) is a clinical syndrome that may manifest itself in non-leg parts of the body as well, called RLS variant, which is considered a distinct entity by some researchers. In this systematic review, we tried to evaluate various clinical features and effective treatments of RLS variants and compare them with that of typical RLS.

Methods: This study was conducted following the PRISMA guideline. The primary search was performed in the data resources of Medline (PubMed), Web of Science, and Scopus, as well as the Google Scholar search engine. The required data were extracted from the studies.

Results: In this review, 1565 studies were initially identified and finally 39 studies were selected. The most common RLS variants were observed to involve hands, head, abdomen, and genitalia. These patients mostly complained of sleep disturbance and feelings of itching, tingling and twitching. Supportive diagnostic criteria of RLS including familial history of RLS, periodic limb movements during sleep (PLMS) and response to treatment with dopaminergic agents were assessed.

Conclusion: It seems that patients with RLS variant can undergo the same diagnostic and therapeutic work-up as patients with conventional RLS. It is suggested that these two disorders fall into the same syndromic spectrum.

1. Introduction

Restless Leg Syndrome (RLS) is diagnosed when all suggestive symptoms, including an urge to move the leg following an unpleasant feeling, onset or exacerbation of symptoms at rest or in the end of the day, alleviation of symptoms by movement, and the absence of other clinical conditions (such as positional discomfort), are present [1]. The prevalence of RLS is about 3% [2,3], and a significant ratio of patients experience depression and suicidal thoughts [4]. The diagnosis of the disorder is mostly clinical and based on the symptoms declared by the patient to the physician; however, it is sometimes difficult to reach a diagnosis even by standard criteria, particularly in those with a severe clinical picture [1]. Sometimes symptoms are paroxysmal or asymmetrical, showing an unusual manifestation of the disease [5]. The single diagnostic sign of RLS is the Periodic Limb Movements of Sleep (PLMS), which is associated with RLS in 80 % of cases [6]. Although this disorder is known as RLS, it may involve other parts of the body as well [1], and when symptoms are exclusively or dominantly present in non-foot body parts, the diagnosis of RLS variant is considered. However, it is required to rule out augmentation in patients with RLS whose symptoms have propagated to other parts of the body [7]. The diagnosis

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of augmentation is indicated when the RLS patient initially responds to dopaminergic agents, but after a while, worsening of symptoms beyond pretreatment levels occurs” [8]. Even when the cases of augmentations are excluded, the occurrence of restlessness symptoms in non-leg body parts is not rare [7], such that a study reported that 6 of 89 RLS cases had RLS variants even after excluding the augmentation cases [7]. Although RLS variants have primarily been investigated in numerous studies, resulting in the understanding of some of its dimensions [9], there is no comprehensive study investigating different aspects of the disease in terms of clinical and therapeutic features so far. In the present review, we tried to address important and generally less studied aspects of RLS variants, including the distribution of symptoms extending to various body parts, supportive diagnostic criteria (including a family history of RLS, response to treatment with dopaminergic agents, the rate of PLMS), the presence of comorbidities, and more detailed sensory and motor symptoms. We aimed to provide readers with coherent and comprehensive information about different RLS variants and the most effective treatments to be used for patient management. For the first time, we here compared different aspects of RLS variants and conventional RLS and assessed the link between these two conditions.

2. Materials and methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [10]. The study’s protocol has been registered at the International Progressive Register of Systematic Review (PROSPERO) databases under the code: CRD4202238345. Based on the PRISMA protocol, the steps of compiling search strategies, screening of studies, selection of studies, quality assessment, and data extraction were performed in the mentioned order. The steps of study selection, quality assessment, and data extraction were independently performed by two researchers, and in the case of any disagreement between these two researchers, the final decision was made through group discussion.

2.1. Databases and search strategy

In the present study, in order to conduct a comprehensive search, the data resources of Medline (PubMed), Web of Science, and Scopus, as well as the Google Scholar search engine were used. Also, proceedings of conferences and congresses and the reference lists of selected studies and systematic reviews were searched to find additional relevant articles. Valid keywords were identified using Medical Subject Headings (MeSH) terms, the keywords of relevant studies, and by consultation with scientific experts. These keywords included: Wittmack-Ekbom Syndrome; Willis Ekbom Disease; Restless Leg Syndrome; Restless Leg Syndrome Variants; Restless Genital Syndrome; and Restless Arm Syndrome.

Using search operators and search fields, search syntax was developed for each of the databases mentioned. The search syntax was initially formulated for the PubMed database; then the syntax formulations for other databases were developed based on that of PubMed. No time limit was applied, and all articles published until the end of December 2022 were searched.

Search syntax in PubMed: (Restless Leg AND (arm OR abdomen OR bladder OR face OR head OR phenotype OR variant))

2.2. Eligibility criteria

All studies investigating the symptoms of RLS involving body parts other than feet and published until the end of September 2022 were included. Exclusion criteria in this study were the symptoms being limited to patients’ legs and the inconsistency of clinical picture with RLS.

2.3. Selection of studies

In order to manage the results of the literature search, all articles were entered into EndNote X20 software. After removing duplicates, the titles and abstracts of the remaining articles were screened based on our eligibility criteria to identify possibly relevant articles, whose full-texts were independently and carefully read by two researchers to finally choose eligible articles.

2.4. Quality assessment and data extraction

Different quality assessment tools were employed according to the methodology of the studies. In this step, two of the researchers independently evaluated the quality of the selected studies using tools such as the Center for Evidence-Based Management (CEMBA) [11] for qualifying case studies and the Axis tool [12] for cross-sectional studies.

Two researchers independently extracted and recorded the information required from the final studies into a pre-prepared checklist, including year of study conduction, place of study conduction, age, gender, description and duration of symptoms, comorbidities, family history, body parts involved, effective treatments, and the rate of PLMS.

3. Results

In this study, 1565 studies were identified in the initial literature search in the databases. After removing duplicates and irrelevant studies and reviewing the titles of articles, 1180 studies entered the screening process. After reviewing the abstracts of these studies, 71 articles entered the next step, and finally, the full-texts of 39 articles were selected for quality assessment and data extraction (Fig. 1).

Distribution of Symptoms in parts of body based on results of this review:

- 1 limbs (fingers, wrist, elbow, arms, toes, legs, and thighs),
- 2 Abdomen (epigastrium, lower abdomen, and the inguinal region)
- 3 Pelvic area (mostly covered the bladder, perineum, anus, buttocks and Coccyx)
- 4 face (all over the face, including the cheek and the entire oral cavity, palate, tongue, and lips)
- 5 The skeletal system (neck (13), shoulder, and waist) (Table 1).

3.1. Results related to supportive diagnostic criteria of RLS

- 1 Familial history of RLS: Information on family history was available in 76 % of the studies, reporting a positive familial history of RLS in 26.4 % of patients.
- 2 Rate of PLMS; 28 % of the studies noted PLMS (mean of 27.8 ± 4.1). In addition to PLMS, depending on the site involved, patients also reported other repetitive movements during sleep, including abdominal jerks, cyclic movements in the abdominal muscle, repeated abdominal rocking, abdominal pressuring by hand, masturbation, and sexual activity during mid-sleep awakenings, rhythmic movements in the trunk and pelvis, and stretching movements of the arm.
- 3 Response to treatment with dopaminergic agents: the most reported effective treatment was Pramipexole. More details are shown in Table 2.

Symptom description (most common symptoms among patients):

- 1 Sleep disturbance: one of the main complaints of patients which was noted in 74 % of the studies
 - 2 Sensation difficulties: the patients most often reported a feeling of restlessness or discomfort, but they could not provide an exact description and described it as a sense of itching, tingling, twitching, formication, cramp and pain.
 - 3 Urge to move: urge to rub the back against the bed, press the back with fingers, rub the face and cheeks, eat food, move the tongue, chew gum, compress teeth, move the arm, and urinate
- the most common comorbidities are summarized in Table 2.

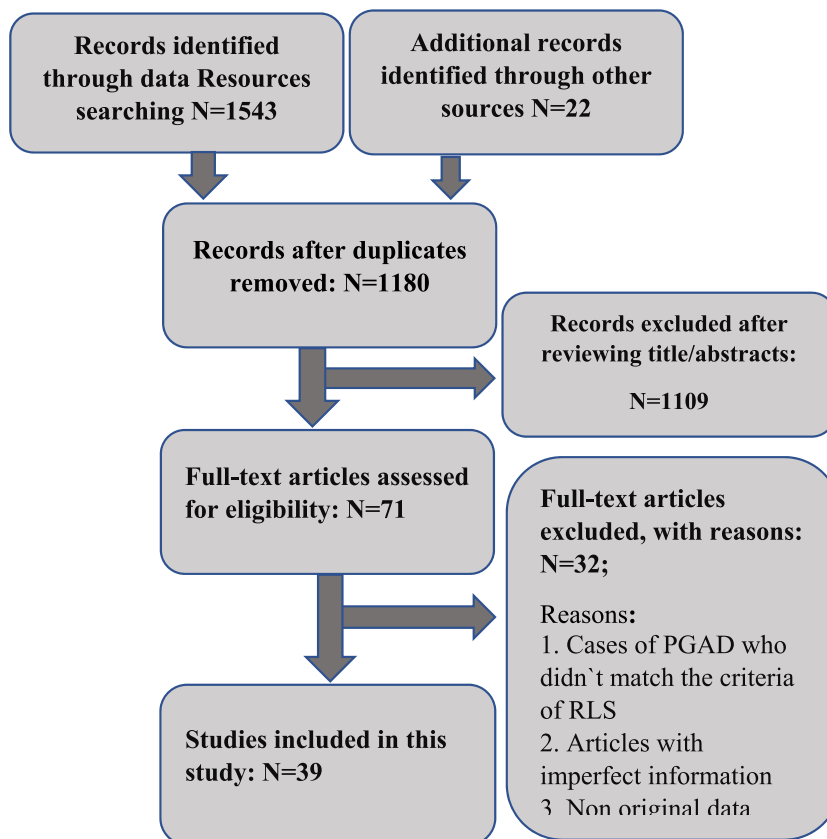


Fig. 1. The flowchart of the studies included in the present systematic review Total number of included patients with RLS variants were 232 patients, that among them 46 (11.7%) of all cases had comorbidity. The mean age of patients with RLS variants was 54.06 ± 9.1 years. Regarding the length of being symptomatic, the minimum was one day, and the maximum was 50 years.

Table 1
The characteristics of the studies included in the present systematic review.

Year country	N	comorbidity	F.H	Main involved organ	Other involved Organs	Effective drug	Main Symptom	PLMS index
2020 China [13]	10	Hypertension: 2 Diabetes: 2 Past anemia: 1 low Iron.S : 5	Yes in 1	Abd	Chest in 1 legs in 5 leg + Arm in 2	Pram gaba Levo/b	insomnia+ (Itching, crawling, numbness, soreness)	23.5 38.2 18.7
2015 Italy [14]	1	many comorbidities Iron.S =NI	Yes	Abd		Pram	'cramps'	No
2014 Japan [15]	1	No Iron.S =NI	no	Abd		Pram	Insomnia + twitching	Yes
2011 Spain [16]	3	hepatitis C in 1, low ferritin in 1	no	Abd	leg in 1	Pram iron preg	Insomnia + twitching, tickling, electric currents	22, 25,35
2020 Korea [17]	4	Hyperlipidemia atherosclerosis Iron.S =NI	Yes in 1	Genitalia	Abd + Legs	Pram Rop,preg IV iron gabap	Insomnia + squeezing, tingling, sexual impulse	-
2017 France [18]	1	no	no	Genitalia	legs	Pram	Insomnia + persistent genital sensation	15
2014 Canada [19]	1	Parkinson disease Iron.S =NI	-	Genitalia	thighs	Pram	Insomnia + congestion, itching, growing of pelvic organs	no
2021 USA [20]	1	Psychiatric disorder Using various medications	-	Genitalia		Tram Pram	genital arousal, urinary symptoms	-
2018 akistan [21]	1	no	-	Genitalia	anus + coccyx	Rop	Insomnia + needle-like sensations	-
2018 Japan [22]	1	After 20 days of milnacipran administration	-	Genitalia	hand + leg + thigh + ingunal	gabap	Insomnia + pain, numbness, vibration	-
2010 Netherlands [23]	1	surgery for a prolapsed uterus appendectomy. Bronchitis/ Iron.S =NI	-	Genitalia	Abd + legs + bladder	Local/A clon	Insomnia + electric currents, preorgasmic feelings urges to void	-
2021 Turkey [24]	1	No/ Iron.S =NI	-	Genitalia	leg	Pram	Insomnia + pulsing, throbbing, itching	-
2003 Italy [25]	1	Facial tic/ Iron.S =NI	no	perineum	Lower Abd + legs	Pram	Insomnia + restless sensation	58
2021 Japan [26]	1	COVID-19	-	perineum	anus	Clon	Insomnia + deep anal discomfort,	-
2018 Japan [27]	1	Parkinson disease	-	perineum	perianal	Pram	Insomnia + perianal restlessness	-
2021 China [28]	1	Schizophrenia MDD	-	arm		-	sleepiness, itch in arms	6
2017S.Korea [29]	1	left thalamic infarction	-	arm		Levo	prickling and pain	-
2012 France [30]	1	focal epilepsy periventricular lesions	-	arm	legs	Pram Iron	Insomnia + pins and needles	-
2012 Brazil [31]	2	-	-	arm		Pram	cramp or inner discomfort	5 in 1
2009 Greece [32]	1	Schizophrenia Iron.S =NI	yes	arm		-	Insomnia + tingling prickling	-
2008 [33]	1	hay fever, asthma	-	arm		Pram	Insomnia + burning and itching	-
2007 USA [34]	1	Iron deficiency COPD, coronary artery disease	-	arm	legs	Pram B. T	Insomnia + twitching wiggling in arms	-
2003 [35]	1	Many comorbidities	no	arm	legs	Rop	Insomnia + twitching, wiggling	32
2000 Canada [36]	112	-	45.3% yes	arm	legs	-	unpleasant sensations	Me = 28.2 ±13.0
2022 Turkey [37]	22	Many comorbidities	-	Head	arm + leg in 18	Pram Rop	numbness, tingling, burning, feeling cold ...	-
2020 India [38]	2	-	-	Head	leg	Levo/c	Insomnia + headache	-
2018 China [39]	2	hypertension in 1 Iron.S =NI	Yes in 1	Back	hip + shoulder in 1 leg in 1	Levo/b	Insomnia + pain, itching discomfort, Soreness, swelling,	-
2010 Japan [40]	1	no	no	Back	Leg + chest + arm	Clon	Insomnia + discomfort	-
2022 Japan [41]	1	NO	-	Back	chest	Pram	Insomnia + dyspnea, discomfort	-

(continued on next page)

Table 1 (continued)

Year country	N	comorbidity	F.H	Main involved organ	Other involved Organs	Effective drug	Main Symptom	PLMS index
2013 Japan [42]	1	Parkinson disease mild renal dysfunction	–	Back		Rop	Insomnia + itching	–
2016 Japan [43]	1	hypertension atrial fibrillation low Hb, low ferritin	no	bladder	Lower Abd + perineum+ +leg	Pram iron Rotig	Insomnia + unpleasant sensation, forced to void	–
2013 Italy [44]	2	–	Yes in 1	bladder	thigh + inguinal cheeks	Pram	Insomnia + force to void	–
2017 Japan [45]	1	BPH Iron.S =NI	no	face		Pram	Insomnia + abnormal sensations	–
2008 USA [46]	1	Hypothyroidism. mild anxiety	yes	face	arm, shoulder + trunk + leg	Meth	tickle, tingling, crawling,	–
1998 Japan [47]	1	end-stage renal disease (ESRD)	–	face		Levo	water-like fluid under facial skin, itching	–
2017 USA [48]	1	fall with trauma to the neck	no	face	Mouth + tongue	Pram	Insomnia+ Swelling, numbness	–
2020 [49] Netherlands	1	(Hb) = 9.5 Iron.S =NI	–	face	arm	Pram	Insomnia + stabbing pain	–
2012 India [50]	5	Low serum Iron Iron.S =NI depression: 2 migraine: 2	– Yes in 3	face face	Tongue + leg Mouth + tongue + leg	Pram Levo/c	tingling sensation Insomnia + burning in mouth	– –
2018 Turkey [13]	1	cervical disc prolapsus, Diabetes	–	Neck	arm	Pram	unpleasant sensation	–

Table 2

The RLS variants comorbidities, and treatments mentioned in the final studies included in the present systematic review.

		Number of articles	Number of cases/dosages
Comorbidity	Hypertension	–	8
	Diabetes	–	7
	Psychiatric disorder	–	7
	migraine	–	5
	Low ferritin	–	5
	anemia	–	4
	Renal dysfunction	–	4
	coronary artery disease	–	3
	Parkinson disease	–	3
Medication	pramipexole	24	0.125–1.5 mg
	levodopa	5	–
	ropinirole	5	0,25- 2 mg
	Iron	4	–
	gabapentin	3	300–600 mg
	clonazepam	3	0.5–1.5 mg
	pregabalin	2	75–150 mg
	tramadol	1	–
	methadone	1	–
	rotigotine	1	2.25 mg

4. Discussion

The present review explored RLS variants. According to the results of the present study, the average age of patients with RLS variant was lower compared to patients with typical RLS, so RLS variants seem to be generally younger. This finding was in line with the reports of previous studies in this area [2,5,7].

In a study in this field, it was shown that the most common body parts involved were the hands, back, abdomen, and buttocks, respectively [7]. Comparison of our results with that of the recent study indicates that the findings are somewhat inconsistent, which may be in part related to the different number of the cases studied in the present study. It is noteworthy that the present study offers a comprehensive and up-to-date view in this field addressing the symptoms dispersed all over the body.

In regard of the supportive diagnostic criteria of RLS, according to the mentioned results, around one-fourth of patients with RLS variant declared a positive family history of RLS. In another study, out of six patients studied, two patients reported a positive family history [7]. The reason for this discrepancy is probably due to the higher number of cases studied in the present study. On the other hand, the family history of RLS among patients seems to vary depending on etiology (i.e., idiopathic vs. secondary) [5,14]. It should be noted that in the present study, the cases of idiopathic and secondary RLS variant have not been discerned from each other. Overall, it can be said that similar ratios of people report a positive family history comparing patients with typical RLS and RLS variant. To our knowledge, this is the first review study reporting the frequency and average rate of PLMS in patients with RLS variant. This

phenomenon was evaluated in only a quarter of those with RLS variant, more than 50% of whom reported PLMS with a moderate severity. Regarding severity, this finding agrees with that observed in RLS patients [15]; however, the prevalence of PLMS has been reported to be higher in RLS patients [5,15]. The lower prevalence of PLMS in RLS variant patients can be related to the incidence of **PLMS equivalents** in these patients. This repetitive and periodic movements reported during sleep includes periodic movements in abdominal wall muscles, masturbation, sexual activity during mid-sleep awakenings, rhythmic movements in the trunk and pelvis, and stretching movements in the arms. In this study, evaluation of the outcomes of pharmaceutical therapy in RLS variant patients revealed that the main prescription drugs resulting in appropriate therapeutic responses included dopamine agonists and then gabaergic drugs. Along with these, iron supplements (oral or injectable) had been used in some cases. These measures are similar to those recommended for RLS patients [5], so it seems that patients with RLS variant can be managed based on RLS therapeutic guidelines.

So far, no comprehensive study has been conducted on the prevalence of comorbidities in RLS variant patients. Here, we portrayed a picture showing a pattern somehow similar to the common clinical conditions observed in patients with typical RLS. In this regard, RLS has been noted to have a strong relationship with iron deficiency and renal disease [16], which was not observed in this study. However, similar to RLS, the variant form of the disease probably is associated with Parkinson's disease [2,17], migraine [16], hypertension [16,18], and diabetes [16]. According to this study, psychiatric diseases are among the most common comorbidities associated with RLS variants. A reciprocal link has been noted between psychiatric diseases and RLS. As well, RLS has been noted to show a strong association with some psychiatric medications [19]. In this study, coronary artery diseases were found to be among common comorbidities in patients with RLS variant; however, findings on the link between RLS and coronary diseases are controversial [18,20,23]. Controversies in this area can be partly due to the limited number of studies on RLS variants compared to typical RLS.

In terms of clinical symptoms, the results of the present study are in line with the reports of studies on RLS. Sleep disturbance was reported in three-quarters of the studies analyzed. In accordance, more than 70% of RLS patients also suffer from sleep disturbance [5]. Moreover, patients with RLS variants often describe their sensations as the feeling of itching, tingling, twitching, formication, cramp, and pain. Also, in RLS patients, the most common descriptions include itching, tingling, burning, and prickling [24]. In both groups of patients, the descriptions imitate neuropathic pain. In response to these unpleasant feelings, RLS patients start walking or moving their legs. Similarly, individuals with RLS variant, depending on the area involved, report an urge to do movements such as rubbing the face, moving the tongue, chewing food or gum, rubbing the back against the ground, moving the arms, urination, and masturbation. Similar to RLS patients, individuals suffering from RLS variant reported repetitive movements in the involved area during rest, such as periodic abdominal movements, sexual arousal, and arm hyperkinetic movements.

There are two different types of assertions about RLS variants. Some consider RLS variants distinct entities from RLS [1], but some others argue that these two disorders can be placed in the same syndromic spectrum [7] and covered under the general term of restless syndrome [7]. According to the results of the present study, RLS and RLS variant are similar in terms of different aspects analyzed in this comprehensive review, so the authors also suggest using the term restless syndrome instead of RLS. Overall, our results indicate that these two disorders fall into the same syndromic spectrum.

5. Limitations and Strengths

The present study was the first comprehensive systematic review on different aspects of RLS variants compared to RLS. One of the limitations of this review was the fact that most studies on RLS variants were case reports, highlighting the need for conducting cross-sectional studies in this area. In accordance with the diagnostic criteria of RLS, only limited studies related to PGAD (RGS) were included in this systematic review, and other studies were excluded.

6. Conclusion

The results of the present study showed that RLS can affect any part of the body. In this study, it was shown that the most commonly involved organs after the legs were the hands, head, abdomen, and genitalia, respectively. The most common complaints of these patients were sleep disturbance and the feelings of itching, tingling, twitching, formication, cramp and pain in the involved body part. Also, patients commonly reported PLMS or its equivalents in various body parts. Similar to RLS patients, the most effective treatment for patients with RLS variant was also dopaminergic drugs (particularly pramipexol). A quarter of patients declared a positive family history of RLS. The most common comorbidities in these patients were also similar to that observed in RLS patients. Overall, it is suggested to screen RLS patients for the occurrence of symptoms in other organs. Moreover, if the RLS variant is diagnosed, the same diagnostic and therapeutic measures used for RLS can be followed. Finally, as RLS, patients with sleep disorders should also be screened for the RLS variants.

Data Availability

Data will be made available on request.

Ethics statement

This systematic review study was approved by Ilam University of Medical Sciences with ethical code IR.MEDILAM.REC.1402.242.

CRedit authorship contribution statement

Mandana Haghshenas: Methodology, Data curation, Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing. **Yousef Veisani:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation. **Ali Sahebi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ali sahebi reports financial support was provided by Ilam University of Medical Sciences. Ali sahebi reports a relationship with Ilam University of Medical Sciences that includes: employment. The authors declare that they have no known competing financial interests.

If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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