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Case Series and Literature Review on Phenotypic Variants of Restless Legs Syndrome (RLS): A Unique Phase of Typical RLS?

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Purpose: The variants of restless legs syndrome (RLS) remain poorly recognized, complicating differential diagnosis and treatment in clinical practice. We aimed to explore the clinical features and potential diagnostic indicators of variant RLS through clinical cases and literature review.

Patients and Methods: Patients with variants of RLS were collected from the sleep medicine center of West China Hospital and followed up till February 2024. Demographic and clinical information were collected, and questionnaires were used to assess RLS symptom severity, sleep disturbances, and daytime dysfunction. Polysomnography and blood tests (eg, iron metabolism) were performed in a subset of cases. A systematic review of literature cases was performed, and comparable data were analyzed.

Results: A total of eight cases (57.0 ± 15.7 years, five females) were enrolled, with half classified as early-onset. Six cases reported isolated abnormal sensations, most commonly in the abdomen, and two had scattered paresthesias involving the legs. Questionnaire rated severe symptoms of variant RLS, night sleep disturbance, and anxiety symptoms in most cases. Dopaminergic agents were effective treatment in seven cases. A literature review of 62 eligible studies (430 cases) confirmed female predominance with the arms most affected. Then, we extracted 70 literature cases, revealed divergent symptoms and early-onset feature in variant RLS. Noteworthily, the periodic limb movement index (PLMI) was abnormal in two-thirds of the cases, but the value in leg-free cases was lower than those which involved legs.

Conclusion: The clinical features and dopaminergic responsiveness of variant RLS closely resembled those of typical RLS, suggesting that existing diagnostic criteria and treatment strategies for typical RLS is applicable to variant phenotypes. Additionally, the PLMI may indicate the potential for variant RLS symptoms progressing to involvement of the legs.

Keywords: restless legs syndrome, variant phenotype, periodic limb movement index, diagnosis, paresthesia

Introduction

Restless legs syndrome (RLS) is a common neurologic sensorimotor disorder, characterized by leg paresthesia and motor restlessness.[1] RLS symptoms were found to present in 9.4% to 15% of the community population,[2] whereas a recent meta-analysis found a confirmed diagnosis of RLS was only 3% in adults.[3] The cardinal clinical features of RLS are the periodic unpleasant or uncomfortable sensations alongside an irresistible urge to move, primarily in the legs, which significantly ameliorates following physical movement.[4,5] These discomforts exhibit the most intensity during the nocturnal phase when resting or inactive.[6] The symptom spectrum of RLS presents with great variability,[7–9] with paresthesia encompassing spontaneous electrical, prickling, burning, tingling, itching, or otherwise odd/indescribable discomfort sensations.[10] Regarding the involved body part, legs are the most affected but not mandatory. Several studies were published and disclosed the arms, calves, trunk, and perineum as RLS equivalents.[11–14] Thereupon, such atypical somatotopic localizations with uncomfortable feelings that mimic RLS have been considered as the phenotypic variants of RLS.[8,15–17]

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The pathophysiology of RLS is multifactorial, involving specific structures of the central nervous system, the dopaminergic system, and iron metabolism.[6] Current findings supported hypothalamus-spinal dopaminergic circuit (A11) regulating the sensorimotor integration and spinal excitability as a central feature, evidenced by RLS symptom relief with dopaminergic agents and exacerbation with dopamine antagonists.[6] Low intracerebral iron store is also implicated, with neuroimaging and post-mortem studies showing that reduced iron concentration in the substantia nigra and basal ganglia is associated to impairing tyrosine hydroxylase and downregulation of dopamine synthesis.[18] In addition, susceptibility loci such as MEIS1, BTBD9, MAP2K5/SKOR1 were identified for the genetic predisposition and family heritability of the RLS.[19] To the variant phenotypes of RLS, the etiopathogenesis was rarely discussed, yet a neuroimage study proposed altered volume of basal ganglia and other structures in limbic system may be associated with the complex morphology in RLS.[20]

However, it is still challenging to recognize the phenotypic variants in clinical practice, especially when the patients have medical comorbidities with overlapped symptoms similar to RLS. Particularly, the objective indicator periodic limb movement index (PLMI) in polysomnography (PSG) is not a must-appear diagnostic criterium in typical adult RLS.[1] At present, the diagnoses of phenotypic RLS variants are primarily made on empirical evidence rather than standardized criteria. Consequently, variant RLS is often underdiagnosed and inappropriately prescribed,[21] due to the heterogeneity of symptom presentations and limited understanding of relevant confounding factors.[22] As a matter of fact, RLS is associated with significant adverse health consequences, such as sleep disturbances[23] and cognitive dysfunctions,[24–27] and even increases the risk of cardiovascular diseases and stroke.[28] Thus, it is necessary to investigate the traits of RLS variants to bridge existing knowledge gaps regarding this underrecognized disorder. In this study, we present eight cases with atypical RLS phenotypes and provide a systematic review of relevant cases in literature.

Materials and Methods

PART I: Clinical Case Series

We consecutively recruited eight patients who met the diagnostic criteria of RLS but with unpleasant or uncomfortable sensations in unusual somatotopic localizations, ie, the paresthesias occur in the somatic region apart from or concurrent with the legs. Nevertheless, when considering differential diagnoses, all potential diseases and medications that may mimic RLS symptoms should be carefully ruled out by specialist physicians prior to the finial diagnosis of variant phenotypes of RLS. Then, all the patients were evaluated and diagnosed by a professional sleep specialist and neurologist (J.Z.), once their symptoms fulfilled the diagnostic criteria of RLS in the International Restless Legs Syndrome Study Group (IRLSSG 2014)[5] or International Classification of Sleep Disorders-Third Edition, Text Revision (ICSD-3-TR),[29] even though the affected body region was out of legs. This study was approved by the West China Hospital of Sichuan University ethics committee and complied with the Declaration of Helsinki. The informed consent was obtained from all participants to publish the medical information in this study.

Demographic information and RLS symptomatologic characteristics (eg, age at onset, somatotopic localizations, abnormal sensations, and family history of RLS among first-degree relatives) were collected. Patients with an age at onset before 45 years old were classified as "early-onset" subtype, otherwise as "late-onset". Comorbid conditions, such as cardiovascular, metabolic, and immunological diseases, were also recorded. Clinical evaluation of RLS severity was completed by the International RLS Rating Scale (IRLS).[30] The total score of IRLS ranges from 0 to 40, of which 0–10, 11–20, 21–30, and 31–40 were labeled as mild, moderate, severe, and very severe level, respectively. The symptoms of anxiety and depression were assessed by the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale −17 (HAMD), and a score >7 in both indicates having clinical anxiety and depression, respectively. Subjective sleep questionnaires including Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI) were used to assess sleep disturbances in patients. ISI was used to evaluate the severity of insomniac symptoms, and a score >14 indicates clinical insomnia (moderate severity). PSQI was applied to assess subjective sleep quality, and a score >5 indicates poor sleep quality. The ESS was used to assess the subjective excessive daytime sleepiness (EDS), and the ESS score >10 is defined as EDS. The Chinese version of above-mentioned scales was obtained and used with appropriate copyright licenses. Overnight PSG was conducted. Laboratory blood tests were conducted including blood routine examination, hepatic and renal function, fasting blood-glucose, lipid, calcium, iron metabolism and thyroid hormones. The final follow-up dates were February 2024.

PART II: Literature Review

Article Selection

Following the PRISMA 2020 guidelines,[31] articles that reported case(s) with variant phenotypic RLS were filtered for a systematic review, with the search term "restless legs syndrome" from PubMed, Web of science, and Cochrane library. Only English peer-reviewed original studies on cases with a confirmed diagnosis of variant type of RLS were included. Studies in which cases had concurrent nervous system complications or other conditions mimicking RLS symptoms were excluded. References cited in retrieved articles were also screened for additional reports. Studies till 31 March 2024 were included (Figure 1).

Literature Case Data Collection

In parallel with our clinical cases, literature cases with "any" variant RLS phenotypes were further extracted from the case report/series of eligible studies. The data concordant to the variables described in clinical cases were extracted for analysis by two independent researchers, which can be reported numerically or graphically, allowing measurement as numerical data.

Statistical Analysis

Statistical analyses on clinical and literature cases were all performed in SPSS software (version 29.0). Quantitative data were presented as "mean ± standard deviation (SD)". Mann–Whitney *U*-tests by ranks were applied to examine the group difference. The Spearman correlation coefficient was used to test the relationships between PLMI and confounding factors. P values <0.05 were considered significant.

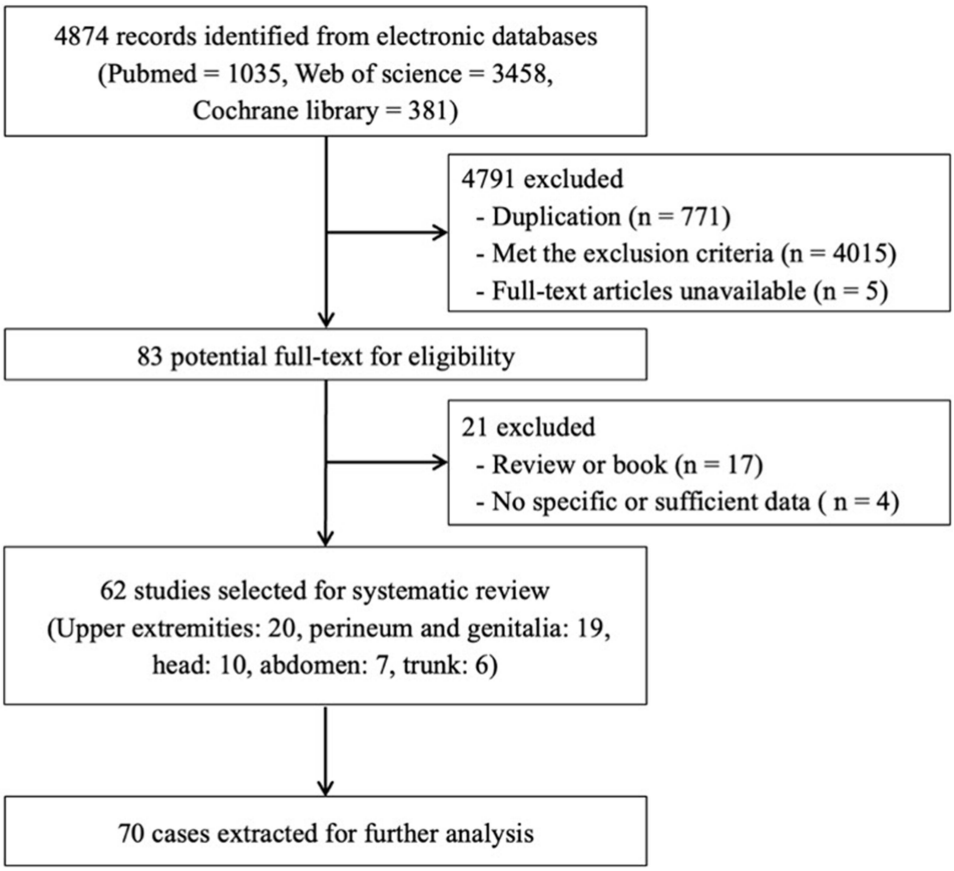

Figure 1 Flowchart of eligible studies and case selection.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. Mar 29 2021;372:n71. doi:10.1136/bmj.n71[31].

Results

PART I: Clinical Variant Phenotypic RLS Cases

Eight cases with variant phenotypic RLS were enrolled in this study, including three males and five females (mean age: 57.0 ± 15.7 years), whereas 50% of the cases were classified as early-onset subtype (onset age < 45 years). Demographic and clinical characteristics of the eight cases are summarized in Table 1. The abnormal sensations and corresponding somatotopic localizations varied substantially across cases. In six patients, the discomfort feelings were fixed in one body region, in which the abdomen is most affected (n = 3) with pain or indescribable discomfort. In the remaining two patients, the paresthesias were scattered across multiple body parts and concurrently involved the legs. Notably, the average diagnostic delay in all cases was 4.63 ± 4.24 years, which was even up to 11 years in two cases with complex or indescribable discomforts. None of the patients had a positive family history of RLS. We performed blood tests assessing iron and glucose metabolism, as well as renal and liver function, to screen for secondary predisposing and precipitating factors in five cases. Four of them represented as low iron status in RLS (ie, serum ferritin ≤ 75ng/mL and transferrin saturation < 45%[32]).

Subjective sleep questionnaires were rated in seven cases. IRLS scores showed that all seven subjects were in moderate and severe RLS levels, and PSQI and ISI scores illustrated poor sleep quality (14.00±3.21) and severe insomniac symptoms (15.57±6.21). Moreover, mood disorders were commonly seen in these variant RLS cases, with a predominance of anxious rather than depressive symptoms (85.71% vs 28.57%). Two cases were confirmed with EDS by the ESS score >10. Laboratory blood examination showed the iron deficiency in one female patient with SLE. One case was assessed by PSG and had a PLMI with 25.7 events/h.

Of note, four cases in our sample had comorbidities which could potentially mimic the RLS symptoms, including systemic lupus erythematosus (SLE), osteoarthritis, and anxiety disorder. All potential confounding causes of RLS-associated symptoms were individually ruled out as follows: *Case 1*: The 34-year-old female patient with generalized nocturnal skin itchiness had a five-year history of SLE, treated with prednisone (5 mg), hydroxychloroquine (400 mg), and tacrolimus (1 mg). The SLE disease was adequately controlled and no active lupus-associated skin lesions were presented, except for the significant iron deficiency (Table 1). The itchiness predominantly occurred at night, subsiding upon getting off the bed but remaining unresponsive to anti-itch cream. A treatment with dopamine agonist in combined preparation with oral iron supplementation resulted in marked improvement of the itchiness within two weeks, then a diagnosis of restless skin was proposed. *Case 6*: The 69-year-old female patient with osteoarthritis was in routine prescribed for methylprednisolone (1mg) and celecoxib (0.2g). The itchiness in ears, mouth, and throat came up approximately 2.5 years after initiating the anti-rheumatic medicine, which mainly happened during bedtime and disturbed sleep. Otorhinolaryngological examinations have been done to exclude the allergic rhinitis, sinusitis, and infections. The diagnosis of restless craniofacial syndrome was then considered by the sleep specialist, and pramipexole (0.25 mg) at bedtime alleviated her symptoms. *Case 7*: The 73-year-old female patient had a history of anxiety disorder, treated with duloxetine (40 mg), clonazepam (0.5 mg), and trazodone (50 mg). She complained of progressively worsened nocturnal urination from 2–3 to 10–20 times per night, which seriously disrupted sleep continuity. She reported no frequent diurnal micturition. The psychiatrist modified the recipe of antipsychotics for her anxiety disorders time and again but with no efficacy. After excluding urological causes (eg, overactive bladder syndrome), restless bladder was diagnosed, and pramipexole (0.25 mg) reduced nocturnal urination to three times per night within weeks. *Case 8*: A 79-year-old female patient suffered severe evening and nocturnal abdominal pain, which was only relieved by walking. A series of physical examinations revealed no structural abnormalities in abdomen to explain the pain. Neither could the symptoms be attributed to an alternate medical condition such as propriospinal myoclonus. Notably, she was diagnosed with RLS decades before, but presented no leg paresthesias in the moment. Her symptoms were poorly controlled with pregabalin (75 mg) but markedly improved after the addition of pramipexole (0.125 mg). Then, a diagnosis of restless abdomen syndrome was made. For the remaining four cases, all necessary examinations were required to comprehensively exclude the causes and conditions that could mimic RLS symptoms, particularly neurological disease and dysfunctions.

The follow-up duration ranged from 5 to 44 months, and the dopaminergic agonists showed satisfied effectiveness in controlling the variant RLS symptoms. Note that irrespective of somatotopic localization, our variant phenotypic RLS subjects were well fitted to the diagnostic criteria of typical RLS in the International Classification of Sleep Disorders-Third Edition, Text Revision (ICDS-3 TR).

Table 1 Demographic and Clinical Information of Eight Cases with Variant RLS

No.	Age (y)/ Gender	Onset Age (y)	Somatotopic Localizations	Abnormal Sensations	Comorbidities	Family History	IRLS	HAMA	HAMD	PSQI	ISI	ESS	Blood Iron Test*	Follow-Up	ICSD-3-TR RLS Diagnostic Criteria
1	34/F	33	Skin of entire body	Itchiness	SLE, lupus mesenteric vasculitis, iron deficiency anemia, hypertension	None	23	13	5	14	15	4	Serum iron: 3.40 umol/L Ferritin: 51.70 ng/mL Transferrin: 2.59 g/L Transferrin saturation: 6.0%	5 months Stopped taking Pramexole (0.125mg) and oral iron supplement after RLS symptoms remitted and no relapse	A: Y (A1: Y, A2: Y, A3: Y) B: Y C: Y
2	41/M	39	Waist and abdomen	Indescribable discomforts	None	None	33	11	7	17	20	9	Increased ferritin**	8 months Suspended Pramexole for ineffectiveness on RLS symptoms and its side effects	A: Y (A1: Y, A2: Y, A3: Y) B: Y C: Y
3	50/M	39	Back trunk, head, and legs	Complex of crush, stretch, and rush	None	None	27	8	8	8	9	5	Serum iron: 22.10 umol/L Ferritin: 203.00 ng/mL Transferrin: 2.17 g/L Transferrin saturation: 44.6%	5 months Pramexole (0.25mg) showed efficiency initially but gradually faded and withdrew after 3 months	A: Y (A1: Y, A2: Y, A3: N) B: Y C: Y
4	55/M	51	Lower cervical vertebra, shoulders, legs, and arms	Coldness	None	None	12	6	6	13	15	0	Serum iron: 33.00 umol/L Ferritin: 419.00 ng/mL Transferrin: 2.47 g/L Transferrin saturation: 62.9% Serum transferring receptor: 0.79 mg/L Erythropoietin: 7.75 mIU/mL	10 months RLS symptoms were controlled by continuously taking Pramexole (0.25mg)	A: Y (A1: Y, A2: Y, A3: Y) B: Y C: Y
5	55/F	44	Lower abdomen	Indescribable discomforts	Hyperlipidemia	None	27	13	6	14	18	11	Serum iron: 15.50 umol/L Ferritin: 132.00 ng/mL Transferrin: 2.37 g/L Transferrin saturation: 34%	6 months RLS symptoms were controlled by Pramexole (0.125mg), but relapsed after withdrew for weeks	A: Y (A1: Y, A2: NA, A3: Y) B: Y C: Y
6	69/F	69	Ears, mouth, and throat	Itchiness	Osteoarthritis, osteoporosis	Unknown	NA	NA	NA	NA	NA	NA	NA	Dropped Pramexole (0.25mg)	A: Y (A1: Y, A2: Y, A3: Y) B: Y C: Y
7	73/F	68	Bladder	Frequent nocturnal micturition without urine	Hypothyroidism, anxiety disorder	None	30	18	7	17	7	3	NA	44 months RLS symptoms were controlled by continuously taking Proamexole (0.25mg) and Alprazolam (0.2mg)	A: Y (A1: Y, A2: Y, A3: Y) B: Y C: Y
8	79/F	76	Abdomen	Painfulness	Chronic non-atrophic gastritis, reflux esophagitis	None	28	15	14	16	25	15	Serum iron: 16.4 umol/L Ferritin: 260.00 ng/mL Transferrin: 2.25 g/L Transferrin saturation: 34% Serum transferring receptor: 1.23 mg/L Erythropoietin: 10.66 mIU/mL	9 months RLS symptoms were improved by continuously taking Pramexole (0.125mg) and Pregabalin (75mg)	A: Y (A1: Y, A2: N, A3: Y) B: Y C: Y

Notes: *Reference ranges of blood iron test if reported: serum iron: 7.8–32.2umol/L; ferritin: 24–336ng/mL; transferrin: 2.5–4.3g/L; transferrin saturation: 20–55%; serum transferring receptor: 0.76–1.76mg/L; and erythropoietin: 3.7–29.5mIU/mL. ** Self-reported by the patient according to the recent test in another lab. ICSD-3-TR RLS Diagnostic criteria: A. complaint of an urge to move the legs, accompanied by uncomfortable and unpleasant sensations that: A1. worse at rest; A2. relief by movements; A3. worse in the evening or nights; B. symptoms not solely accounted for by a condition that mimics RLS; C. the symptoms of RLS cause concern, distress, sleep disturbance, or impairment. The presence of periodic leg movements during sleep, a family history of RLS, and response to dopaminergic therapy support a diagnosis of RLS.

Abbreviations: BMI, Body mass index; RLS, restless legs syndrome; PLMI, periodic limb movement index; IRLS, International RLS Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD-17, Hamilton Depression Scale −17 items; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; N, no; NA, not available; Y, yes.

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PART II: Literature Review on Variant Phenotypic RLS

A total of 62 studies encompassing 430 cases of variant RLS from 19 countries were included, with Japan contributing the most publications (see Figure 2 and Supplementary Table 1). Restless arms were the most frequently reported phenotype (233 cases, 20 studies), followed by perineum and genitalia variants, primarily observed in females. Within the eligible studies, gender information was available for 322 cases, revealing a female predominance (male:female = 1:1.9). Among the 210 cases with precise somatotopic localization of paresthesias, the most affected body regions were the arm, abdomen, and trunk in males, and the perineum/genitalia, hands, and head in females (see Figure 3).

Additionally, we filtered out 70 subjects, who had comparable data with our clinical cases, and aggregated the data on clinical characteristics and questionnaire scores. Within this sample, 55.7% were male, and 48.4% were the early-onset

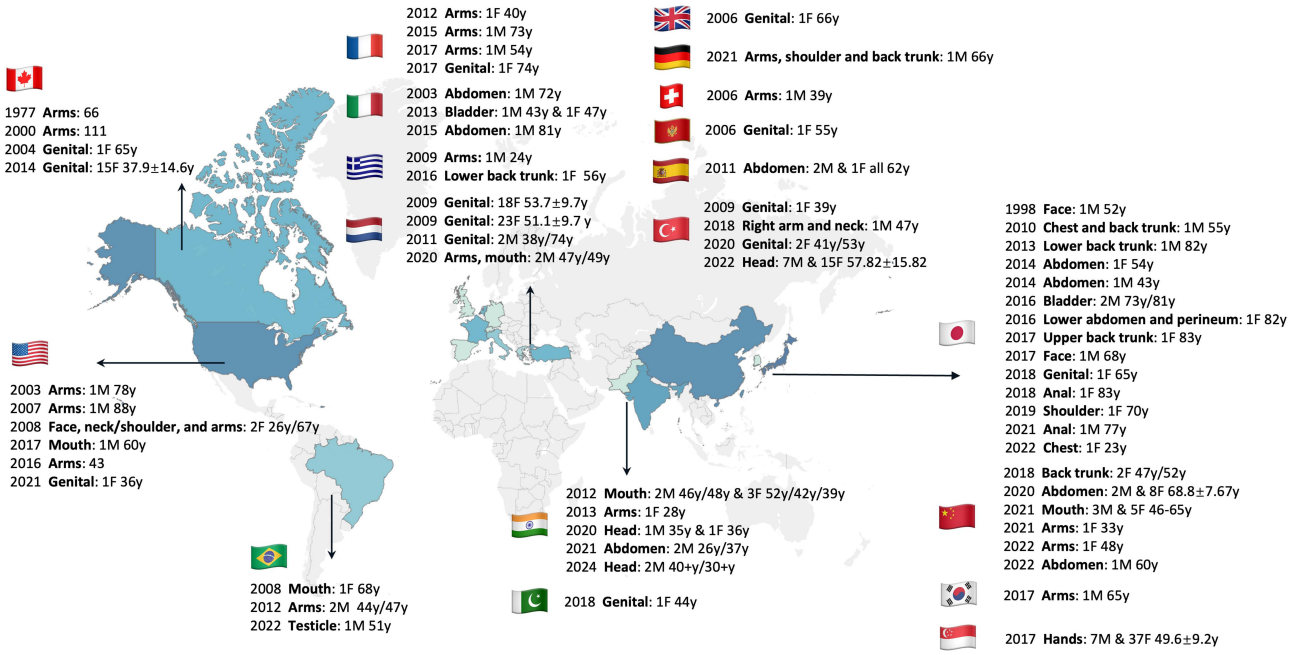

Figure 2 Lists of included articles and the epidemiology of variant RLS cases.
Abbreviations: F, female; M, male; Y, year(s).

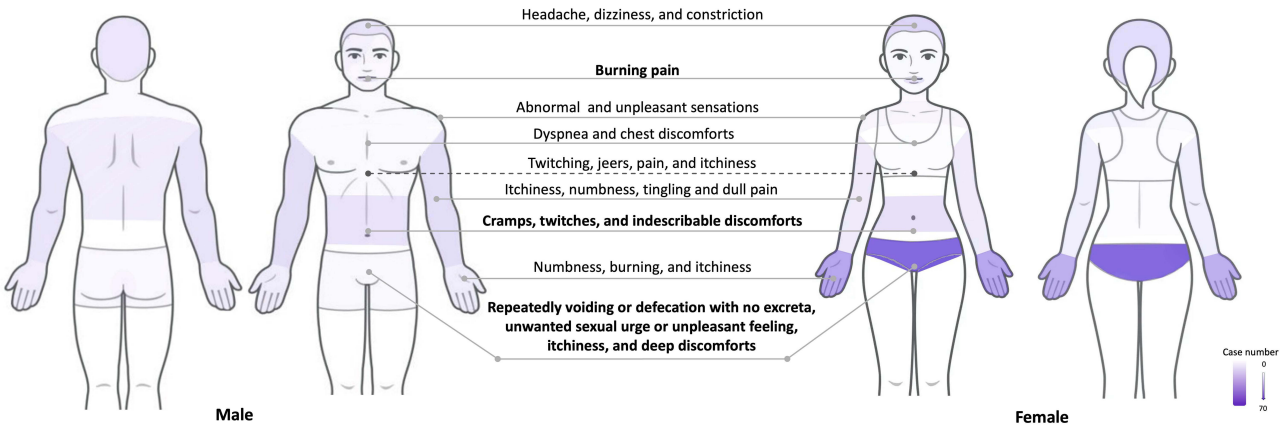

Figure 3 Body diagram of paresthesia in the variant RLS by gender.
Notes: This body diagram showed the corresponding location of abnormal sensation in 210 variant RLS patients from literature review. The intensity of the color represents the number of patients, eg, a darker color indicates the more cases had abnormal sensations in the corresponding body part. By gender, the arm, abdomen, and back trunk were the three most affected body parts in males, whereas perineum and genitalia, hand, and head were in females. Burring pain in restless mouth, cramps twitches and dull pain in restless abdomen, and repeated voiding or defecation, unwanted sexual urge or itchiness in restless perineum and genitalia were more consistently reported.

subtype. Most patients experienced a diagnostic delay of ≤5 years (74.6%), and follow-up duration was <1 year (80%). Only 25.6% reported a family history of RLS, yet 90% were classified as severe RLS (ie, IRLS score >20). The specific sensations of RLS variants primarily presented as burning pain in the restless mouth, cramps, twitches and dull pain in the restless abdomen, and repeated voiding or defecation, unwanted sexual urge or itchiness in the restless perineum and genitalia (see Figure 3). Notably, 62.9% of cases had abnormal sensations co-occurring in the legs. Iron deficiency was uncommon (12.1%), and most patients (79.5%) received dopaminergic agents with positive therapeutic responses.

Furthermore, we extracted the PLMI from 12 literature cases (23 ± 18.52 events/h), with 58.3% exceeding 15 events/h. Importantly, in the leg-free variant RLS cases, 50% had a PLMI greater than 5 events/h. Cases with concurrent leg discomfort (n = 6) had a significantly higher PLMI compared to those without leg involvement (n = 6) (36.33 ± 14.36 vs 9.67 ± 11.04, p = 0.0087). Spearman correlation analyses showed no significant correlation between PLMI and age onset (n = 11, r = 0.28, p >0.05), or disease duration (n = 11, r = −0.34, p >0.05).

Discussion

The current study reported eight cases with variant phenotypes of RLS and systematically reviewed the relevant literature. We confirmed the female preponderance similar to typical RLS and demonstrated divergent symptomology across different somatotopic localizations in the variant RLS. Remarkably, we reinforced that the diagnostic criteria of RLS in ICSD-3-TR is feasible for diagnosing variant RLS phenotypes, and dopaminergic agent is an effective therapeutic approach. In addition, PLMI can be an alternative objective indicator in recognizing variant RLS, albeit with limited data.

Currently, the diagnostic criteria for phenotypic variants of RLS are not yet formally authorized, but they are instead regarded as the empirical equivalents of typical RLS. The diversiform paresthesias in variant RLS often involve separate body regions and multiple organ systems. Whereas many other diseases, such as burning mouth syndrome, irritable bowel syndrome, and peripheral neuropathy, could manifest symptoms mimicking the variant RLS. Such phenotypic variety of variant RLS requires clinicians to familiarize themselves with these complicated conditions and direct comprehensive, in-depth differential diagnosis. Especially to the general practitioners or primary care settings, physicians should be vigilant to the existence of such variant phenotypes when evaluating patients presenting with insomnia and unexplained nocturnal paresthesias. As known, typical RLS has significant negative impact on daytime function, while rarely studied in variant RLS. There were only three studies which investigated mood problems in the reviewed literature.[17,33,34] We found severe anxious and depressive symptoms, as well as daytime sleepiness in our variant RLS cases. Thus, the adverse consequences should be taken into consideration to support the diagnosis of variant RLS. However, in clinical practice, the variant RLS is always an exclusion diagnosis after ruling out the usual diseases presenting symptoms similar to RLS,[1] which could lead to a serious delay, up to decades in some cases.[35–37]

RLS is a multifactorial condition involved in genetic risk, environmental factors, and comorbidities. In our analysis, the RLS family history and causative comorbidities for secondary RLS (eg, iron deficiency or kidney disease) were infrequent in the two parallel samples, but nearly half the cases were early-onset subtype. As known, early-onset RLS is often associated with genetic pathogenesis, while late-onset subtype is more ascribed to comorbidities. Evidence suggests that iron deficiency is the primary reason for typical RLS onset and the progression,[38] which may disturb the synthesis and modulation of dopaminergic motor circuits in supraspine.[39] Approximately 13% of cases had iron deficiency in the aggregated variant RLS samples from the literature review. Yet, according to the consensus[32] and updated algorithm of RLS management,[40] 80% (4/5) of our clinical cases met criteria of iron therapy (serum ferritin concentration ≤ 75 ng/mL and transferrin saturation < 45%), suggesting insufficient intracerebral iron store in these patients with variant RLS. In typical RLS, low intracerebral iron store has been linked to reduced tyrosine hydroxylase activity and downregulated dopamine receptors in brain regions such as the substantia nigra and striatum.[41] This dopaminergic dysregulation leads to inappropriate inhibitory signals and high-threshold muscle afferents in the legs; consequently, the leg muscles were consistently activated and causes uncomfortable sensations with the urge to move for relief, eg, periodic leg movements.[42]

The pathophysiology underlying the RLS paresthesias locations remains incompletely understood, and no single hypothesis can fully explain the heterogeneous nature of variant RLS. Nevertheless, several previous studies have discussed the potential sensorimotor pathways, particularly those involving supraspinal hyperexcitability, may contribute to the sensations.[43] From findings in animal research, the dopaminergic diencephalospinal tract has the longest axons

projecting to the spinal dorsal horn, which is more vulnerable to stress and then the damages in integrity move upward toward shorter axons.[44] The above-mentioned injury pattern of spinal dopamine terminal can lead to caudal-to-rostral degeneration and predominant leg symptoms in RLS.[45] Consequently, different anatomical substrates (including cervical, thoracic and lumbar levels) were supposed to be affected in the variant phenotypes.[46] Intriguingly, a previous study reported PLMI in anterior tibialis and extensor digitorum brevis muscles (PAMI) in three RLS patients involved with both arms and legs. These results showed a higher PLMI (88.4 events/h) than PAMI (55.2 events/h) during sleep, and the muscle activities in electromyography were asynchronous between legs and arms.[47] Moreover, the PLMI has been approved to correlate positively to the severity of RLS.[48] In the current study, we found 50% of the leg-free variant RLS cases had PLMI greater than 5 events/h, and then the cases involved with legs had significantly higher PLMI than those without. Based on these findings, we may assume that the PLMI is an objective indicator for leg-free variant RLS, which implies the ongoing spread of the paresthesias to legs. The increased PLMI may suggest that multiple body parts would be involved during the progression of the broader context of RLS. Further, we may consider that the PSG is still valuable in diagnosing variant RLS, especially for the cases with complicated or ambiguous clinical history. Yet, up to date, PLMI in overnight PSG is not mandatory for the diagnosis of typical RLS, rather a supportive indicator, especially in cases with ambiguous clinical history. As well, PLMI was rarely studied in variant RLS, then no finding was reported on the role of PLMI in the RLS cases not involving legs. On the other hand, estrogens were reported to protect the dopaminergic neurons in the nigrostriatal,[49] which could explain the female preponderance in variant RLS. Dopaminergic agents showed optimal therapeutic effects in the variant cases, indicating they shared a common pathogenesis with typical RLS. Still, it remains unjustified whether these variant cases are equivalents of typical RLS regarding to the pathophysiological mechanism. In future, large multicenter studies are required to verify our findings.

Several limitations should be noted. First, our clinical sample size was relatively small, including eight cases of variant RLS, which may limit the generalizability of our findings. However, given that this an uncommon medical condition, the majority of previous studies on variant RLS have also included small samples. Second, the literature review was subjected to considerable data heterogeneity, attributing to the variations in study design, diagnostic approaches, and reported clinical details. Third, a potential diagnostic ambiguity may exist in variant RLS due to the lack of objective diagnostic indicators and overlapping symptoms with other disorders. Finally, the indication of PLMI in variant RLS was confined to the limited available data in literature review.

Conclusion

In summary, variant RLS tends to onset in early age with a female predominance, which also manifests diverse phenotypes challenging the accurate diagnosis. Yet, typical RLS diagnostic criteria remain applicable in recognizing variant RLS in clinical practice, and the elevated PLMI may indicate the symptom spreading to the lower extremities.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, Junying Zhou by zhoujy2016@scu.edu.cn.

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Author Contributions

Xinyan Zhang: Data curation, Methodology, Investigation, Visualization, Validation, Software, Formal analysis, Writing – original draft, Writing – review & editing; Xue Zhou: Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing; Yangyang Shen: Software, Writing – review & editing; Jiafeng Ren: Data curation, Writing – review & editing; Weifang Yin: Data curation, Writing – review & editing; Hongxin Mi: Software, Writing – review & editing; Junying Zhou: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – original draft, Writing – review & editing.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; all authors took part in drafting, revising or critically reviewing the article; all authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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