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REVIEW

Unraveling Restless Legs Syndrome: A Comprehensive Review of Current Research and Future Directions

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Abstract: Restless leg syndrome (RLS) is a prevalent neurosensory motor disorder that significantly affects the quality of life of patients. This article provides a comprehensive review of advancements in RLS research encompassing epidemiology, genetics, pathophysiology, diagnostic methodologies, and treatment approaches. Epidemiological investigations have established the global prevalence of RLS, highlighting variations in age, sex, and race, and their association with medical conditions such as pregnancy, anemia, and chronic kidney disease. Genetic research has concentrated on familial inheritance patterns, the functions of associated genes, and the interplay between genetic predispositions and environmental influences. Pathophysiological studies have examined the involvement of the central nervous system, dopaminergic system, and neurotransmitter imbalances in the etiology of RLS. The diagnostic techniques discussed include the progression of clinical diagnostic criteria, application of imaging modalities, laboratory examinations, such as serum ferritin assessment, and identification of biomarkers. Treatment strategies encompass both pharmacological and non-pharmacological interventions along with the exploration of personalized treatment options. Furthermore, this article anticipates the integration of emerging technologies in RLS research, the increasing trend of interdisciplinary collaboration, and the challenges and opportunities that future research may encounter with the objective of providing a thorough reference for advanced research and clinical practice concerning RLS.

Keywords: RLS, dopamine, neurotransmitter, dopamine receptor agonists, TCM

Introduction

Restless legs syndrome (RLS), also referred to as Willis-Ekbom disease, is a common neurological sensorimotor disorder characterized by an uncontrollable urge to move the legs, typically accompanied by uncomfortable sensations, particularly during periods of rest or night.[1] These symptoms often disrupt sleep and negatively affect the quality of life. RLS affects individuals across age groups and populations and frequently occurs in association with comorbid conditions, such as pregnancy, chronic kidney disease, and iron deficiency.[1] Despite its prevalence, RLS remains underdiagnosed and is often misattributed to other disorders, thereby delaying appropriate management.[2]

The etiology of RLS is multifactorial, involving genetic predisposition, iron dysregulation, and disturbances in dopaminergic and glutamatergic neurotransmission.[3] Advances in neuroimaging, genetics, and neurophysiology have deepened our understanding of the underlying mechanisms, and multiple genome-wide association studies (GWAS) have identified susceptibility loci that support heritable components.[4] Clinical research has contributed to the refinement of diagnostic criteria and development of both pharmacological and non-pharmacological treatment strategies. Nevertheless, substantial gaps remain in our mechanistic knowledge, the identification of reliable biomarkers, and the management of treatment-related complications, such as augmentation.

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Several fundamental contributions have guided the development of RLS research.[1] The earliest formal description is attributed to Karl-Axel Ekbom, who coined the term "restless legs" in the 1940s and established the syndrome as a distinct clinical entity through a systematic case series.[5] His work laid the foundation for modern diagnostic criteria and emphasized the sensorimotor nature of the disorder. In the 1980s and the 1990s, Montplaisir et al advanced the classification of RLS by identifying its strong association with periodic limb movements (PLM) during sleep (PLMS), linking RLS to the broader category of sleep-related movement disorders.[6] In the early 2000s, Earley and Connor proposed an influential iron-dopamine model, positing that brain iron deficiency impairs dopaminergic function, a hypothesis that remains central to the current pathophysiological frameworks.[7] In parallel, family based linkage analyses and the first GWAS published in 2007 by Winkelmann et al identified MEIS1 and BTBD9 as genetic risk loci, marking a turning point in our molecular understanding of RLS.[8]

In this review, we provide a comprehensive synthesis of the current state of RLS research encompassing epidemiological patterns, genetic findings, pathophysiological mechanisms, diagnostic advancements, and evolving treatment paradigms. We also highlight the emerging technologies and interdisciplinary trends that are poised to shape the future of RLS research and clinical management. By integrating recent discoveries with foundational knowledge, this review aims to provide a broad, yet critical resource for both clinicians and researchers in the field.

Epidemiological Basis of Restless Legs Syndrome

Global Prevalence of Restless Legs Syndrome

RLS is a globally prevalent disorder with notable disparities observed across regions and populations. A systematic review and modeling analysis published in 2019 estimated the global prevalence of RLS among adults aged 20–79 years at 7.12%, corresponding to approximately 356.07 million affected individuals worldwide.[9] The prevalence was comparable between countries with high and low-to-medium sociodemographic indices (H-SDI and LM-SDI), recorded at 7.29% and 7.10%, respectively;[10] however, over 90% of cases (323.06 million) were located in LM-SDI regions, largely due to population size. Europe reported the highest prevalence rates, whereas the lowest estimates were observed in Africa.[9] The Western Pacific region, including parts of East Asia, has also demonstrated an elevated prevalence. In North American and Western European populations, the prevalence among adults has been reported to range from 4% to 29%.[11]

Despite these comprehensive estimates, epidemiological studies in several regions remain underrepresented. In Asia, reported prevalence varies from 1.0% to 7.2%,[12] with studies in South Korea documenting rates around 3.5% and Chinese pediatric populations showing rates of 2.2–2.4% depending on age group.[13] The Middle East has shown higher prevalence estimates, with population-based studies from Saudi Arabia and Iran indicating rates between 8% and 12%, particularly elevated in pregnant cohorts.[14] In Latin America, limited data from Brazil and Mexico suggest a prevalence range of approximately 5%–10%, with higher rates noted among individuals with diabetes and chronic kidney disease,[12] underscores the need for more regionally diverse studies employing standardized diagnostic frameworks to fully elucidate the global burden of RLS.

The prevalence varies significantly across demographic and clinical populations. For instance, during pregnancy, symptom onset frequently occurs in the third trimester.[15] A study of 260 pregnant women reported a peak RLS prevalence of 26.5% in the third trimester, which declined to 18.1% at two months postpartum and 7.3% at six months, closely aligned with the 6.2% observed in a non-pregnant control population.[15] Among patients undergoing maintenance hemodialysis, a meta-analysis incorporating 57 studies and 12,573 participants reported a pooled prevalence of 24.0%, with notably higher rates among women and patients in the Americas, as well as a trend of increasing prevalence over time.[16] These findings reinforce the importance of recognizing high-risk subpopulations and accordingly tailoring diagnostic and preventive strategies.

Analysis of the Incidence of Restless Legs Syndrome in Different Age Groups

Although RLS has been observed across various age groups, its incidence varies significantly. Research indicates a notable prevalence among children and adolescents. For instance, a study conducted on students aged 10 to 19 years in Turkey revealed a definitive diagnosis rate of RLS of 2.74%, with a higher prevalence in females (3.42%) than in

males (2.04%).[17] A longitudinal investigation involving 1856 Canadian children aged 7–15 years reported an annual prevalence of RLS ranging from 2.4% to 3.1%.[18] Notably, the prevalence among boys surpassed that among girls at the age of 12 years, with an overall occurrence of RLS of 8.6% at any point during the study period. Furthermore, children with an affected parent exhibit a higher prevalence (13.0%) than those without (6.9%).[18] In Henan, China, the overall prevalence of RLS among students aged 8–17 years was 2.2%, with rates of 1.8% in the 8–11 age group and 2.4% in the 12–17 age group. Additionally, the prevalence was greater in females (2.7%) than in males (1.7%) and increased with age.[19] These findings indicate that RLS is relatively common among children and adolescents, with potential variations depending on the sex and age.

The elderly population is also at a heightened risk for RLS.[20] An assessment of 1012 outpatients aged > 65 years in Turkey identified a prevalence of 10.18% for RLS, with only nine individuals previously diagnosed with the condition.[20] The mean duration of symptoms was reported as 4.80 ± 4.65 years, and 26.2% of the patients had a positive family history. Additionally, a survey conducted in South Korea among individuals over 65 years of age indicated a prevalence of RLS of 9.5% (7.1% in men and 11.3% in women), with significant associations identified between RLS and conditions such as anemia and kidney disease.[20] These studies underscore the necessity for enhanced screening and diagnostic efforts for RLS in the elderly, particularly among those with related comorbidities.

Gender and Racial Differences in Restless Legs Syndrome

Research indicates a notable sex disparity in the prevalence of RLS, with a higher incidence observed in females, with numerous studies demonstrating that women are approximately twice as likely to develop RLS as men.[21] For instance, a retrospective study of 42 women and 42 men diagnosed with RLS revealed that women exhibited more severe symptoms.[22] The findings were corroborated by assessments using the International RLS Study Group Severity Scale (IRLS), RLS-6, and Clinical Global Impression (CGI) scores, all of which indicated that women experienced more pronounced symptoms and had lower serum ferritin levels than their male counterparts.[22] Furthermore, the prevalence of RLS is notably elevated during pregnancy, which can be attributed to various factors.[23] A study conducted among pregnant women in Saudi Arabia reported a prevalence rate of 30% for RLS, which was not significantly different from that observed in nonpregnant women (26.5%). However, the incidence of severe or very severe RLS was 25% in the pregnant women compared to 15% in the control group. Multivariate analysis identified parity, anemia, diabetes, vitamin D deficiency, and smoking as independent predictors of RLS.[23]

Although the body of research on racial differences is limited, existing studies have suggested variability in the prevalence and clinical manifestations of RLS across different racial groups. A study involving 359 patients with RLS in China indicated that subjective experiences reported by patients differed from those documented in Western populations, with Chinese patients describing less pain, increased soreness, and a higher prevalence of iron deficiency, along with seasonal fluctuations and absence of anemia.[24] Additionally, an investigation into treatment-seeking behaviors across ethnic groups revealed that African Americans were disproportionately represented among untreated RLS patients (44.8% vs 8.6%), with patients receiving treatment being more likely to regard RLS as a serious medical condition with considerable psychosocial implications.[25] These differences may be influenced by a multitude of factors, including genetic predisposition, environmental conditions, and lifestyle choices, warranting further investigations.

Genetic Study of Restless Legs Syndrome

Familial Genetic Model of Restless Legs Syndrome

RLS exhibits significant familial aggregation, with over 50% of affected individuals reporting a family history of the condition.[26] Numerous studies have suggested that the inheritance pattern may be autosomal dominant. For instance, one study documented a family with exclusively female RLS patients, comprising seven individuals aged between 12 and 59 years, with a mean age of 35.3 ± 14.4 years. Genetic analysis has indicated an autosomal dominant mode of inheritance.[26] Additional studies involving multiple, large families have corroborated this inheritance pattern. Furthermore, twin studies have demonstrated a higher concordance rate for RLS in monozygotic twins than in dizygotic twins, underscoring the significant influence of genetic factors on RLS morbidity.[3]

However, the genetic underpinnings of RLS are complex and cannot be attributed to a straightforward single-gene inheritance model. GWAS has identified several genetic loci associated with an increased risk of RLS; however, these common variants account for only a minor portion of the overall disease risk.[4,8] For example, variations in genes such as MEIS1 and BTBD9 have been linked to RLS; however, known risk variants explain only a limited aspect of genetic susceptibility to the disorder.[27] In addition, rare genetic variants may contribute significantly to RLS morbidity. Whole-exome sequencing conducted on a German family with RLS revealed novel variants in PCDHA3, WWC2, ATRN, and FAT2 that co-segregated with the condition, indicating that these genes may be potential candidates for RLS.[28] Collectively, these findings illustrate the complexity of the genetic architecture of RLS and highlight the need for further research to elucidate its genetic mechanisms.

Identification and Functional Analysis of Related Genes

Numerous genes associated with RLS have been identified through GWAS, with MEIS1, BTBD9, and PTPRD recognized as the most significantly correlated candidate genes.[3] Research on MEIS1 revealed the presence of rare alleles in a cohort of 188 patients and 182 controls, followed by genotyping of approximately 3000 patients and 3000 controls, along with functional analyses of the identified variants using an in vivo neurogenesis model.[29] These findings indicate a notable increase in rare variants of MEIS1 in patients with RLS. Furthermore, functional analyses have demonstrated that the majority of these variants are loss-of-function alleles that impair the functionality of typical MEIS1 splice isoforms, thereby establishing a connection between the loss of MEIS1 function and the etiology and pathology of RLS.[29]

BTBD9 has garnered considerable interest in the scientific community, with research indicating that knockout of this gene in murine models produces a phenotype analogous to RLS.[30] In the nematode Caenorhabditis elegans, deletion of the homologous gene hpo-9 results in hyperoviposition. Furthermore, genetic interaction analyses involving dopamine receptor genes (DOP-1 and DOP-3) revealed that hpo-9 exerted effects comparable to those of DOP-1, whereas its deletion significantly elevated the expression of DOP-3.[30] In BTBD9 knockout mice, there was a notable increase in D2 receptor (D2R) mRNA, a marked reduction in D2R protein levels, and an increase in Dynamin I within the striatum. These findings suggest that BTBD9 may play a role in the pathophysiology of RLS by influencing the dopaminergic system.[30] Collectively, these investigations of the functions of related genes offer valuable insights into the underlying mechanisms that contribute to RLS morbidity.

Interaction Between Genetic Factors and Environmental Factors

The prevalence of RLS is attributed to the interplay between genetic and environmental factors. Various genetic variants that increase an individual's susceptibility to RLS have been identified.[31] Environmental factors, including lifestyle choices and nutritional status, may modulate genetic predispositions. Notably, iron deficiency is a significant environmental contributor to RLS, and genetic factors potentially influence an individual's vulnerability to iron deficiency and the expression of genes associated with iron metabolism.[32] Research has demonstrated that sensorimotor symptoms analogous to those of RLS manifest in experimental models of iron deficiency, leading to alterations in dopaminergic, glutamatergic, and adenosinergic neurotransmission,[33] suggesting a complex interaction between iron deficiency and genetic factors that affect morbidity associated with RLS.

Moreover, additional environmental factors, such as tobacco use, alcohol consumption, and sleep disorders, may interact with genetic predispositions.[9] A study involving patients with RLS indicated that smoking is correlated with an elevated risk of developing RLS and that genetic factors may influence an individual's response to such environmental exposures, thereby affecting the overall risk of RLS morbidity.[9] Nevertheless, the precise mechanisms underlying the interactions between genetic and environmental factors remain poorly understood, necessitating further investigation to elucidate this intricate relationship and to establish a more comprehensive theoretical framework for the prevention and treatment of RLS.

Integrative Interpretation of GWAS Findings and Functional Implications

GWAS have identified several genetic regions that increase the risk of RLS, with MEIS1, BTBD9, and PTPRD being the most consistently reported in both European and Asian populations.[3,27] Among these, MEIS1 shows the strongest and

most consistent association, particularly with variants such as rs12469063 and rs2300478, with reported odds ratios ranging from 1.6 to 2.5 depending on the study population.[34] Functional studies have shown that certain MEIS1 variants reduce the normal activity of genes in neural development models and interfere with iron regulation in the brain, supporting its role in both neurodevelopment and iron-related pathways relevant to RLS.[29]

BTBD9 is another key gene identified by GWAS that has been validated in both human and animal studies.[35] In BTBD9 knockout mice, researchers observed symptoms similar to RLS, including disrupted sleep and excessive limb movements, along with increased D2 dopamine receptor mRNA, but reduced protein levels in the striatum, suggesting that BTBD9 may affect dopamine signaling through post-transcriptional mechanisms.[30] Studies in *Caenorhabditis elegans* have shown that removing the homologous gene hpo-9 alters dopamine receptor gene expression and motor function, further supporting BTBD9's involvement in RLS.[30] PTPRD, a gene involved in maintaining connections between nerve cells (synaptic adhesion) and regulating synaptic strength, has also been associated with RLS in GWAS.[36] It is expressed in brain regions relevant to movement control, such as the striatum and spinal cord, although its exact biological role in the RLS remains unclear.

Despite these findings, the known genetic variants account for only a small fraction of the overall genetic contribution to RLS (less than 10%).[3] Additionally, many of these variants are located in the non-coding regions of the genome, making it difficult to determine how they influence disease risk. To better understand the biological effects of these genetic variants, future research should integrate GWAS data with other molecular analyses, such as gene expression profiling, epigenetic mapping, and chromatin accessibility studies. Moreover, few studies have explored how these genes interact with each other or with environmental factors, particularly in non-European populations. Although GWAS has significantly expanded our understanding of genetic risk in RLS, further functional studies and multi-omics research are needed to clarify how these findings can lead to new diagnostic or therapeutic strategies.

Pathophysiological Mechanism of Restless Legs Syndrome

Role of Central Nervous System in Restless Legs Syndrome

The central nervous system (CNS) is an integral part of RLS pathophysiology. Numerous studies have identified various CNS abnormalities in individuals with RLS, including alterations in nerve excitability, neurotransmitter imbalances, and modifications to both brain structure and function.[37] From the perspective of neural excitability, research utilizing neurophysiological techniques has suggested that RLS should be regarded as a complex sensorimotor disorder characterized by a dysfunctional network involving cortical, subcortical, spinal, and peripheral nerve generators, resulting in heightened excitability and/or diminished inhibition.[37] For instance, investigations of spinal cord excitability in patients with RLS have revealed increased excitability, indicating that the spinal cord may contribute significantly to the pathogenesis of RLS. However, inconsistencies in sensory assessments and reflex analyses suggest that alterations in spinal cord excitability may exhibit heterogeneity.[38]

Regarding brain structure and function, iron deficiency has been observed in the brains of individuals with RLS, correlating with decreased myelination.[33] Autopsy and imaging studies comparing brain tissue from RLS patients and control subjects have demonstrated a reduction of approximately 25% in the expression of myelin-associated proteins, such as myelin basic protein (MBP), proteolipid protein (PLP), and the oligodendrocyte-specific enzyme 35-cyclic nucleotide phosphohydrolase (CNPase) in RLS patients.[39] Additionally, significant reductions in iron transport proteins, including transferrin (Tf) and H-ferritin (H-Frt), were observed in the myelin sheath. Imaging analyses have also indicated a slight but significant reduction in white matter volume in regions such as the corpus callosum, anterior cingulate gyrus, and precentral gyrus, suggesting that brain iron deficiency may contribute to myelin loss and impair nerve conduction, thus playing a role in the morbidity of RLS.[39] Furthermore, functional magnetic resonance imaging (fMRI) and related studies have identified functional abnormalities in multiple brain regions, including the thalamus, sensorimotor cortex, and cerebellum, thereby reinforcing the critical involvement of the CNS in the pathogenesis of RLS.

The Relationship Between Dopamine System and Restless Legs Syndrome

Dysfunction of the dopamine system is a significant hypothesis for the pathophysiology of RLS. Numerous studies have demonstrated that dopaminergic medications can alleviate RLS symptoms, whereas dopamine receptor antagonists tend to exacerbate these symptoms, indicating critical involvement of the dopamine system in RLS.[30,33] For instance, research involving RLS patients has shown that treatment with dopamine agonists, such as pramipexole and ropinirole, results in symptom improvement, suggesting that abnormalities within the dopamine system may be a primary contributor to RLS morbidity.[40]

Further investigations have revealed alterations in dopamine transporter (DAT) levels in patients with RLS.[41] Utilizing (11)C-methamphetamine and positron emission tomography (PET) techniques to assess DAT binding potential in the striatum, researchers found that DAT binding in patients with RLS was significantly lower than that in control subjects, with reductions observed in the putamen and caudate, but not in the ventral striatum. This finding implies a potential decrease in membrane-bound striatal DAT, which may impair dopamine transport and function, thereby contributing to the manifestation of RLS symptoms.[41] Additionally, animal studies have provided further evidence supporting the association between dopamine system dysfunction and RLS, particularly through the observation of biochemical changes in the dopaminergic system in iron-deficient rodent models, similar to those observed in RLS patients.[33] This further substantiates the hypothesis that dopamine system dysfunction plays a pivotal role in morbidity associated with RLS.

Neurotransmitter Imbalance Mechanism of Restless Legs Syndrome

In addition to the dopamine system, imbalances in other neurotransmitters contribute to morbidity associated with RLS. Notably, disruption of glutamatergic neurotransmission has garnered significant attention.[40] Research indicates that individuals with RLS exhibit abnormalities in glutamatergic signaling, which may result in hyperexcitability. Furthermore, alterations in both dopaminergic and glutamatergic systems have been observed in rodent models of iron deficiency, suggesting a potential link between iron deficiency and RLS morbidity through its impact on glutamatergic neurotransmission.[40]

Moreover, γ-aminobutyric acid (GABA), a principal inhibitory neurotransmitter in the central nervous system, is gaining recognition.[42] Proton magnetic resonance spectroscopy analyses of patients with RLS revealed no significant differences in the levels of GABA, glutamate, and N-acetylaspartate (NAA) in the thalamus, cerebellum, and dorsal anterior cingulate cortex between patients and control subjects.[43] However, within the RLS cohort, GABA levels in the thalamus were positively correlated with PLM and RLS severity, whereas a negative correlation was observed in the cerebellum, suggesting that GABA may influence the sensory and motor manifestations of RLS by modulating the interactions between the cerebellum and thalamus.[27] The investigation of these neurotransmitter imbalances offers a comprehensive framework for enhancing our understanding of the mechanisms underlying RLS morbidity, and aids in the development of more effective therapeutic strategies.

Integrated Neurochemical Network and the Central Role of Iron Deficiency

The pathophysiology of RLS is now increasingly understood as a result of complex interactions among multiple neurotransmitter systems rather than isolated dopaminergic dysfunction, with players in this neurochemical network including the dopaminergic, glutamatergic, GABAergic, and adenosinergic systems, whose coordinated imbalance contributes to the heterogeneous manifestations of RLS.[44]

Iron deficiency plays a central upstream role in neurotransmitter synthesis, transport, and synaptic regulation. As a cofactor for tyrosine hydroxylase, iron is essential for dopamine synthesis, and its deficiency reduces dopamine production and DAT activity, thereby disrupting synaptic dopamine homeostasis.[45] Simultaneously, animal models and neuroimaging studies have indicated that iron deficiency alters glutamatergic and adenosinergic signaling. In particular, increased thalamic glutamate levels observed via proton magnetic resonance spectroscopy (1H-MRS) may exacerbate sensory hyperexcitability and sleep disturbances.[46] Concurrently, reduced adenosine A1 receptor activity in iron-deficient states can disinhibit glutamate release and disturb dopaminergic regulation.

GABAergic pathways, which are essential for motor inhibition, may fail to counterbalance this excitatory drive.[47] Regional alterations in GABA levels, especially within the thalamus and cerebellum, have been linked to the severity of RLS symptoms and PLMs.[48] These findings underscore a dynamic imbalance between the excitatory (glutamatergic) and inhibitory (GABAergic) systems, which are further modulated by adenosine and dopamine pathways.

This integrative framework highlights iron deficiency as a converging pathogenic factor that disrupts neurochemical balance across multiple axes. This also explains why monotherapies targeting a single neurotransmitter often yield incomplete symptom control, thereby supporting the rationale for multimodal therapeutic strategies aimed at restoring iron homeostasis and neurotransmitter equilibrium.

Diagnostic Techniques for Restless Legs Syndrome

Evolution of Clinical Diagnostic Criteria

The diagnostic framework for RLS has undergone multiple revisions over the past few decades, paralleling advances in clinical characterization and mechanistic understanding. Early diagnostic efforts were largely based on subjective symptom reports with significant variability in terminology and clinical interpretation. A major milestone was achieved in 1995 when the International Restless Legs Syndrome Study Group (IRLSSG) introduced a formal set of diagnostic criteria aimed at standardizing clinical recognition.[49] These criteria emphasize four core features: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night; and (5) the symptoms are not solely accounted for by another medical or behavioral condition, such as leg cramps, positional discomfort, myalgia, venous stasis, or habitual foot tapping.[50]

Subsequent revisions in 2003 and 2012 aimed to improve diagnostic specificity and reduce misclassification, particularly in the research context. The 2012 update reaffirmed the four essential criteria and added guidance for distinguishing RLS from clinical mimics, such as positional discomfort, myalgia, or peripheral neuropathy. To enhance diagnostic confidence, a set of supportive clinical features was introduced, including a positive family history, presence of PLMs during sleep, response to dopaminergic therapy, and absence of sensory deficits on neurological examination.[50]

The diagnostic criteria for RLS have also been extended to pediatric populations, where symptom descriptions are often vague or behaviorally inferred.[51] In such cases, accurate diagnosis relies heavily on parental observation and the use of an age-appropriate language. While these adaptations have improved the recognition of RLS in children, it is important to emphasize that the overall prevalence of RLS in pediatric populations remains significantly lower than in adults.[51] This distinction is essential for the accurate clinical interpretation and assessment of public health. Nevertheless, challenges remain, as atypical presentations and comorbidities can obscure classical features and variability exists in how clinicians apply these criteria. Future updates to diagnostic standards may benefit from incorporating objective tools, such as neurophysiological testing or imaging, to improve the accuracy in younger patients.

Progress in Imaging Diagnosis of Restless Legs Syndrome

Imaging modalities are crucial tools for diagnosing and understanding morbidity associated with RLS. Magnetic Resonance Imaging (MRI) has been extensively employed in research on RLS.[52] Structural MRI investigations have identified notable alterations in the brain structures of individuals with RLS.[39] For instance, voxel-based morphometry (VBM) analyses have demonstrated a reduction in white matter volume within the corpus callosum, anterior cingulate gyrus, and precentral gyrus in patients with RLS, suggesting the presence of structural abnormalities such as myelin sheath degradation. This finding is consistent with the decrease in myelin-associated proteins observed in postmortem examinations.[39]

fMRI studies have revealed functional abnormalities in the brain of patients with RLS. Research indicates that these individuals exhibit pathological activation across various regions of the sensorimotor and limbic networks, implying that these areas may significantly contribute to the morbidity of RLS by influencing the manifestation of sensory and motor symptoms as well as emotional regulation.[53] Furthermore, proton magnetic resonance spectroscopy (MRS) studies have

corroborated the presence of abnormalities in the limbic system of RLS patients, indicating a disruption in glutamatergic neurotransmission, which further substantiates the hypothesis of neurotransmitter imbalance in the pathophysiology of RLS.[53] Nevertheless, there is considerable heterogeneity in the findings of the current imaging studies, with variations potentially attributable to methodological differences and sample characteristics. Therefore, it is imperative to refine the study design to enhance the consistency and reliability of results.

Application of Biomarkers in the Diagnosis of Restless Legs Syndrome

The identification of effective biomarkers for early diagnosis and monitoring of RLS is of paramount importance. Current research has investigated the potential of various biomarkers in the diagnosis of RLS. For instance, glycomic analysis conducted on serum samples from RLS patients identified 24 N-glycan biomarker candidates that exhibited significant differences when compared to control subjects, as determined by liquid chromatography-mass spectrometry (LC-MS /MS).[54] Notably, specific partial glycan structures, including HexNAc6Hex8Fuc1NeuAc2, HexNAc6Hex6Fuc1NeuAc3, and HexNAc5Hex6Fuc1NeuAc2, demonstrated the most pronounced alterations in their expression profiles, suggesting their potential utility as biomarkers for RLS diagnosis.[54]

Furthermore, the neurofilament light chain (NfL) has emerged as a biomarker with diagnostic relevance in various neurological disorders. In the context of RLS, research has indicated that while serum levels of NfL did not show significant differences between RLS patients and control groups, nor were they significantly correlated with disease duration or severity, larger-scale studies are needed to further elucidate its role in RLS.[55] Additional investigations have assessed other potential indicators, such as the F-wave duration and periodic limb movement index (PLMI), which may have diagnostic value for RLS. However, further research is necessary to validate and refine the application of these biomarkers to enhance the accuracy and specificity of RLS diagnosis.

Treatment Strategies for Restless Legs Syndrome

The Latest Progress in Drug Therapy

Pharmacological interventions for RLS are primarily focused on alleviating symptoms and enhancing the overall quality of life of the affected individuals. Currently, first-line therapeutic agents predominantly consist of dopamine receptor agonists and α2δ calcium channel ligands.[44] Dopamine receptor agonists, including pramipexole, ropinirole, and rotigotine, activate dopamine receptors and modulate the dopaminergic system, thereby mitigating RLS symptoms.[56] Numerous randomized controlled trials have demonstrated the significant efficacy of these dopamine agonists in ameliorating RLS symptoms, as evidenced by a marked reduction in IRLS scores, a decrease in PLMI during sleep, and an enhancement in both sleep quality and overall quality of life in patients.[57,58] However, long-term administration of dopamine agonists may lead to complications, such as symptom exacerbation, diminished efficacy, and augmentation, which present challenges in the management of the condition.

In recent years, the therapeutic potential of α2δ calcium channel ligands such as gabapentin and pregabalin has gained prominence in the treatment of RLS. Research indicates that these agents are effective in alleviating RLS symptoms and may offer superior safety and tolerability profiles compared to dopamine agonists.[59] For instance, pregabalin has demonstrated efficacy in the management of RLS and has shown favorable safety outcomes in long-term treatment scenarios extending up to one year.[59] Furthermore, in cases of severe RLS in which first-line treatment is ineffective, the use of opioids such as tramadol, oxycodone, and methadone may be considered. Although these opioids can provide symptomatic relief, it is crucial to remain vigilant regarding the potential risks associated with their use, including addiction. There remains a pressing need to develop more effective pharmacological options that exhibit fewer side effects to adequately address the treatment requirements of patients with RLS.

Clinical Application of Non-Drug Therapy

Nonpharmacological interventions play a supportive role in the management of RLS, particularly for patients with mild symptoms, those intolerant to pharmacologic agents, and individuals seeking adjunctive treatments.[60] Structured physical exercise has been increasingly recognized for its therapeutic potential. Meta-analyses have demonstrated that both

aerobic and resistance training significantly reduce symptom severity and improve sleep and overall quality of life in individuals with RLS.[60] Exercise programs involving moderate-intensity activity performed three to five times per week have been associated with reductions in motor restlessness, improved mood, and reduced fatigue.[61] These effects are believed to result from enhanced dopaminergic transmission, improved peripheral circulation, and modulation of the central nervous system excitability.

In addition, certain behavioral therapies, such as massage and warm water baths, have shown symptom-alleviating effects.[62] These approaches are thought to promote muscle relaxation and vascular perfusion, thereby reducing discomfort and facilitating sleep. For instance, regular leg massage has been reported to decrease leg sensations and improve sleep quality in some patients.[62]

Furthermore, neuromodulatory physical therapy modalities, including repetitive transcranial magnetic stimulation (rTMS) and transcutaneous direct current spinal cord stimulation (tsDCS), are being explored for their utility in RLS treatment.[63] Studies have shown that tsDCS may enhance sleep quality and reduce RLS symptoms. In a study involving 15 patients, tsDCS reduced the fractional amplitude of low-frequency fluctuations (fALFF) in the right anterior insular/temporal pole and decreased regional homogeneity (ReHo) in the supplementary motor area.[64] Concurrently, changes in weighted degree centrality (DC)—specifically, an increase in the left primary visual cortex and a decrease in the right posterior cerebellum—were correlated with clinical improvement, suggesting that tsDCS may exert therapeutic effects through modulation of neural network activity.[64]

Despite encouraging findings, most nonpharmacological therapies remain in the exploratory phase. Further high-quality randomized controlled trials are necessary to validate their efficacy, establish standardized protocols, and better define their role in integrated treatment strategies for RLS.

Exploration of Individualized Treatment Plan

Owing to variability in symptoms, severity, genetic predispositions, and treatment responses among patients with RLS, it is essential to investigate personalized treatment strategies. When formulating a treatment plan, comprehensive assessment of various patient-specific factors is necessary. For instance, in individuals with iron deficiency, iron replacement therapy may serve as a critical component of treatment, and iron supplementation can rectify abnormal iron metabolism and alleviate RLS symptoms in certain patients, indicating that iron-deficient patients with RLS often experience significant symptom relief after iron supplementation.[50]

Moreover, treatment customization based on the genetic profiles of patients has garnered increasing attention. Advances in the genetic understanding of RLS have revealed that certain genetic variations may influence patients' responses to pharmacological interventions. For example, individuals with specific genetic variants may exhibit varying degrees of efficacy when treated with dopamine agonists.[30,45,57] Consequently, utilizing genetic testing to ascertain patients' genetic backgrounds can facilitate the selection of more suitable therapeutic agents and dosages, thereby enhancing the precision and effectiveness of treatment. Nonetheless, the implementation of personalized treatment faces several challenges, including the high costs associated with genetic testing and the complexities involved in interpreting test results.[65] These issues necessitate further research and technological advancements to promote the integration of personalized treatment approaches in the management of RLS.

Clinical Practice of Traditional Chinese Medicine (TCM) in the Treatment of Restless Legs Syndrome

TCM operates within a unique theoretical framework that differs from the Western biomedical paradigms. Central to TCM is the concept of qi, which refers to the vital energy circulating through the meridians of the body and is essential for maintaining physiological balance.[66] Disorders such as RLS are often interpreted within TCM as arising from deficiencies or imbalances in qi and blood or dysfunctions of the liver and kidney systems.[67] Clinical diagnoses may involve terms such as "qi and blood deficiency" or "tendon and vessel dystrophy", which reflect the syndromic patterns derived from these principles. Thus, treatment strategies, such as herbal formulations and acupuncture, are directed at restoring systemic harmony based on syndrome differentiation rather than targeting a specific pathological mechanism.[68]

A systematic review and meta-analysis focusing on the Shaoyao Gancao Decoction indicated that this traditional formulation may help alleviate RLS symptoms; however, the overall quality of evidence was low, highlighting the need for further rigorous validation.[69] Another comprehensive review of 85 studies on TCM interventions for RLS identified more than 40 unique prescriptions comprising 176 different herbal components. Although some of these prescriptions were associated with symptom improvement, most studies lacked methodological rigor; only nine included control groups and only three were randomized controlled trials.[70] In a few of these trials, TCM interventions appeared to outperform Western medicine in relieving symptoms.[71] Nevertheless, methodological limitations, such as inconsistent use of Western diagnostic criteria and reliance on unvalidated self-report scales, raise concerns regarding the reliability of the outcomes. In summary, although TCM presents potential therapeutic value for RLS, high-quality randomized controlled trials are needed to confirm its efficacy.

Taking Shaoyao Gancao Decoction as a case study, some reports indicate that patients experienced significant relief from leg discomfort and improved sleep quality following its administration.[72] One patient, who presented with symptoms of leg soreness, heaviness, and nocturnal insomnia, was diagnosed with qi and blood deficiency and tendon and vessel dystrophy according to TCM principles and subsequently treated with a modified version of the Shaoyao Gancao Decoction.[70] After a period of treatment, the patient's symptoms gradually improved. Additionally, acupuncture and moxibustion have been employed in conjunction with TCM, targeting specific acupoints, such as Zusanli and Sanyinjiao.[73] This combined approach aimed at regulating qi and blood has been reported to lead to significant symptom alleviation in patients with RLS. These individual case studies suggest that TCM may offer specific advantages in the treatment of RLS through tailored syndrome differentiation, acupoint selection, and medication. However, the limitations inherent in case studies preclude the generalization of these findings, underscoring the need for larger-scale research.

TCM is generally regarded as a safe treatment option for RLS. Studies examining various TCM prescriptions for RLS have reported relatively fewer adverse reactions.[69,70] Nonetheless, the limited quality of most studies may hinder the comprehensive assessment of safety. Certain TCM formulations, particularly those aimed at promoting blood circulation and alleviating blood stasis, may pose potential risks to coagulation; however, reports specifically related to RLS are scarce. Caution is warranted regarding potential drug interactions, particularly when TCM is concurrently used with modern pharmacological treatments. For instance, the co-administration of TCM with dopaminergic medications may influence their efficacy or increase the risk of adverse effects. In summary, current evidence suggests that TCM is generally safe for the treatment of RLS; however, further high-quality studies are essential to elucidate its long-term safety profile.

Guideline-Based Recommendations and Management of Treatment Complications

Recent consensus guidelines published by the IRLSSG provide a structured algorithm for the pharmacological treatment of RLS, with an emphasis on risk stratification, iron status, and augmentation prevention.[74] These guidelines recommend α2δ calcium channel ligands (eg, gabapentin and pregabalin) as first-line agents, especially in patients with comorbid insomnia, anxiety, or pain, owing to a lower risk of augmentation compared to dopaminergic therapies.[49,75]

Dopamine receptor agonists, including pramipexole, ropinirole, and rotigotine, are effective for short-term symptom control, but are associated with a well-documented risk of augmentation.[58] Augmentation refers to a drug-induced paradoxical worsening of RLS symptoms, often presenting as an earlier onset of symptoms in the day, increased symptom severity, or spread to other body parts.[76] According to IRLSSG guidelines, the risk of augmentation increases with higher doses (>0.5 mg/day for pramipexole or >4 mg/day for ropinirole), prolonged use, and evening or multiple daily dosing.[77] The 10-year cumulative incidence of augmentation with dopamine agonists has been reported to exceed 60% in some cohorts.[59]

When augmentation occurs, management includes dose reduction, switching to α2δ ligands, or use of long-acting opioids in refractory cases.[78] Levodopa, although effective for transient relief, is associated with an even higher risk of early augmentation and is generally discouraged from long-term use.[79]

Iron deficiency is a key factor that can be modified. IRLSSG and subsequent clinical studies recommend initiating iron replacement therapy when serum ferritin is <75 ng/mL and <100 ng/mL if symptoms are severe or refractory, respectively. Intravenous iron formulations, such as ferric carboxymaltose or iron sucrose, are preferred over oral iron for patients with

gastrointestinal intolerance or insufficient response. A randomized controlled trial demonstrated significant symptom reduction with IV iron administration in patients with serum ferritin levels <75 ng/mL, supporting this approach.[33,80]

Taken together, these evidence-based strategies reinforce the importance of individualized therapy based on symptom severity, iron status, and risk of augmentation. Incorporating guideline-informed decision making may improve long-term outcomes and reduce adverse treatment effects.

Future Prospects of Restless Legs Syndrome Research

Application of Emerging Technologies in the Study of Restless Legs Syndrome

Emerging technologies present novel opportunities for investigating RLS. Recent studies have indicated that electronic stimulation may serve as a promising nonpharmacological intervention for RLS. A randomized, single-blind trial involving 46 patients with RLS assessed the efficacy of electronic stimulation (ES) by dividing the participants into active and sham stimulation groups. Utilizing a handheld ES device, the lower legs were stimulated bilaterally in a 3 Hz tapping pattern. The results demonstrated a significant reduction in symptom severity within the active group accompanied by a notable interaction between time and group. These findings suggest that ES may enhance symptom relief when applied at optimal stimulation intensities, positioning it as a potential non-pharmacological treatment alternative for RLS.[81]

Noninvasive high-frequency peroneal nerve stimulation (NPNS) offers an innovative approach for RLS management. Research involving 20 patients with moderate-to-severe RLS revealed that NPNS effectively alleviated symptoms by activating the leg muscles without disrupting sleep. This study indicated that NPNS could sustain tonic electromyographic (EMG) activity over time, with evoked EMG responses serving as predictors of treatment efficacy. Notably, improvements in the IRLS scores were more pronounced in patients with lower motor thresholds. Additionally, NPNS treatment frequently enhances patients' self-reported sleep onset.[82] As these emerging technologies continue to evolve and improve, they are expected to yield more effective therapeutic options for individuals with RLS.

The Trend of Interdisciplinary Research on Restless Legs Syndrome

Research on RLS has demonstrated a notable interdisciplinary trend. Given that RLS encompasses various domains including neurology, psychology, and genetics, it is challenging to fully elucidate the mechanisms of morbidity and identify effective treatment modalities within a single discipline. For instance, integration of neuroscience and psychology can enhance our understanding of how psychosocial factors influence RLS. A qualitative analysis of 15 patients with RLS revealed that stigma associated with the loss of physical control and insufficient professional recognition contributed to psychological distress, underscoring the significance of psychosocial elements in the diagnosis and treatment of RLS as well as the necessity for interdisciplinary collaboration in patient care.[83]

Furthermore, epidemiological-genetic crossover studies utilizing extensive population studies and genetic analyses can provide more precise insights into the genetic predisposition and environmental risk factors associated with RLS. Additionally, interdisciplinary research fosters the amalgamation of diverse technologies and methodologies, such as the integration of imaging techniques with molecular biology, facilitating a comprehensive investigation of the relationships between brain structure, function, neurotransmitter activity, and gene expression in individuals with RLS. Interdisciplinary research is anticipated to yield significant advancements in our understanding of RLS and contribute to the development of effective treatment strategies.

Challenges and Opportunities for Future Research

Although significant progress has been made in the understanding of RLS, several important challenges remain in research and clinical practice. From an epidemiological perspective, RLS is known to affect a large number of people worldwide, with differences observed across age, sex, and ethnic groups.[84] However, large-scale studies from underrepresented regions are lacking, and the influence of cultural and social factors on symptom reporting and treatment choices is not well understood.

In terms of genetics, studies have identified several risk genes, although these may only explain a small portion of cases. The exact mechanisms by which these genes contribute to RLS symptoms, especially how they affect brain

function or iron metabolism, remain unclear. In addition, the interaction between genetic background and environmental factors, such as iron levels, diet, and lifestyle, requires further investigation.

At the biological level, RLS appears to involve imbalances in several brain signaling systems, including dopamine, glutamate, GABA, and adenosine. These changes are often linked to iron deficiency in the brain, which may affect the nerve activity and sleep regulation. However, it is still uncertain how these systems interact and whether one disturbance leads to another disturbance. Further research is needed to understand how changes in brain structure, function, and neurotransmitter levels contribute to the development and progression of RLS.

Currently, the diagnosis of RLS still depends mainly on the symptoms reported by patients. Although imaging and blood-based studies have suggested possible biomarkers, none has been widely accepted or used in clinical practice. There is a clear need to identify accurate and practical tests that can help confirm the diagnosis and distinguish RLS from other similar conditions. In addition, current treatments can be effective for many patients but are often limited by side effects or worsening symptoms over time. Although non-drug treatments and TCM may help in some cases, most studies in this area have not met rigorous scientific standards, and more high-quality research is needed to confirm their effectiveness and safety.

Despite these challenges, new technologies offer several opportunities. For example, gene editing may help to clarify how certain genes affect RLS and could lead to gene-based treatments. Artificial intelligence could help researchers analyze large datasets to discover better diagnostic tools or identify new treatment targets. Encouraging collaboration across disciplines, including neurology, genetics, pharmacology, and traditional medicine, is important for developing more effective strategies to understand and manage RLS in the future.

Conclusion

In summary, RLS is a multifactorial neurological disorder with a substantial global burden that exhibits notable variations in prevalence across age groups, sexes, and ethnic populations. Although genetic studies have identified several susceptibility loci, such as MEIS1, BTBD9, and PTPRD, these account for only a small proportion of the heritability, indicating that the genetic architecture of RLS remains incompletely understood. At the pathophysiological level, iron deficiency is thought to play a central role in interacting with the dopaminergic, glutamatergic, GABAergic, and adenosinergic systems to disrupt neurochemical homeostasis and contribute to symptom generation.

Advancements in diagnostic approaches have led to the refinement of clinical criteria and increased utilization of neuroimaging modalities. However, the lack of objective and universally accepted biomarkers continues to limit early and accurate diagnosis. Therapeutically, dopaminergic agents and α2δ calcium channel ligands remain the mainstay of pharmacological treatment, while non-pharmacological interventions, such as neuromodulation and behavioral therapies, provide additional benefits, particularly for patients with contraindications or poor tolerability to medications. Nonetheless, the long-term use of pharmacological agents is often constrained by risks such as augmentation and reduced efficacy.

TCM, including herbal formulations and acupuncture, has shown potential in alleviating symptoms in certain patients; however, the current evidence is limited by methodological shortcomings and the absence of standardized outcome measures. To improve clinical management and deepen mechanistic insight, future research should prioritize the integration of multi-omics analyses, identification of reliable biomarkers, and execution of well-designed clinical trials to evaluate emerging and complementary therapies. Thus, advancing the diagnosis, treatment, and prevention of RLS will require a more comprehensive and interdisciplinary approach, with future research benefiting from systematic reviews and meta-analyses to synthesize existing evidence, resolve inconsistencies, and inform evidence-based clinical practices.

Abbreviations

RLS, restless legs syndrome; IRLS, International Restless Legs Syndrome Study Group Severity Scale; CGI, Clinical Global Impression; GWAS, genome-wide association studies; D2R, D2 receptor; CNS, central nervous system; MBP, myelin basic protein; PLP, proteolipid protein; CNPase, cyclic nucleotide phosphohydrolase; Tf, transferrin; H-Frt, H-ferritin; fMRI, functional magnetic resonance imaging; DAT, dopamine transporter; PET, positron emission tomography; GABA, γ-aminobutyric acid; NAA, N-acetylaspartate; PLM, periodic limb movements; MRI, Magnetic

Resonance Imaging; VBM, voxel-based morphometry; MRS, magnetic resonance spectroscopy; NfL, neurofilament light chain; PLMI, periodic limb movement index; rTMS, repetitive transcranial magnetic stimulation; tsDCS, transcutaneous direct current spinal cord stimulation; fALFF, fractional amplitude of low-frequency fluctuation; ReHo, regional homogeneity; DC, degree centrality; TCM, traditional Chinese medicine; ES, electronic stimulation; NPNS, noninvasive high-frequency peroneal nerve stimulation; EMG, electromyographic.

Disclosure

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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