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Review

Restless legs syndrome in multiple sclerosis: A call for better understanding and non-pharmacological management

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ABSTRACT

Multiple sclerosis (MS) affects an estimated 400,000 people in the United States and results in a number of outcomes, including cognitive and motor dysfunction, symptoms of fatigue, pain and depression, comorbidity, and compromised quality of life. There is emerging evidence that restless legs syndrome (RLS) is another manifestation of MS, yet there is minimal research to date investigating safe and efficacious management of RLS within the MS population. This paper provides a broad overview of RLS, focuses on RLS in MS, and proposes an agenda for future research that includes rehabilitation as a non-pharmacological approach for the management of RLS in MS.

KEYWORDS: restless legs syndrome, multiple sclerosis, rehabilitation, exercise

1. Introduction

Multiple sclerosis (MS) is an immune-mediated, demyelinating disease of the central nervous system (CNS) with an estimated prevalence of 400,000 persons in the United States. This disease results in a number of outcomes, including cognitive and motor dysfunction, symptoms of fatigue, pain and depression, comorbidity, and compromised quality of life. There is recent interest in restless legs syndrome (RLS) as another consequence of MS [1-3]. One paper reviewed the prevalence, correlates, and consequences, particularly sleep and fatigue, of RLS in MS, and further provided a research agenda focusing on the course of RLS in MS and its management through disease-modifying therapies and pharmacology [4]. We take a fresh look at RLS in MS by first focusing on a broad review of its definition, diagnosis, measurement, epidemiology, and pathophysiology, patient consequences and burden, and management using pharmacology and rehabilitation, and then focusing on similar issues in MS. One central theme of this paper is the focus on managing RLS in MS using exercise training as a symptomatic, rehabilitation strategy. This paper concludes with an agenda and clarion call for future research that includes non-pharmacological rehabilitation approaches for managing RLS in MS.

2. Restless legs syndrome

2.1. Definition

RLS, or Willis-Ekbom Disease, was originally described in 1943 by Karl Ekbom as “paresthesia in the legs” or “irritable legs” [5]. The National Institute for Neurological Disorders and Stroke defines it as “a neurological disorder characterized by throbbing, pulling, creeping, or other unpleasant sensations in the legs and an uncontrollable, and sometimes overwhelming, urge to move them” [6]. These symptoms most commonly occur (a) in the lower extremities and, on occasion, the head, trunk, and upper extremities, and (b) at night, when the individual is at rest, frequently resulting in difficulty sleeping or staying asleep. Movement of the area experiencing symptoms can provide temporary relief, but symptoms generally persist when the individual

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returns to a resting condition. The etiology of RLS is unknown, but there are two recognized forms of RLS, namely idiopathic RLS and secondary RLS. Idiopathic RLS is most commonly reported in the general population, whereas secondary RLS is generally reported in clinical populations.

2.2. Diagnosis

Physicians typically rely upon subjective ratings for the diagnosis of RLS. This necessitates standardized criteria that can be applied by clinicians for consistent diagnosis, and the criteria for diagnosis were initially established by the International Restless Legs Syndrome Study Group (IRLSSG Diagnostic Criteria) [7, 8]. The criteria, which yielded a four-part questionnaire, establishes that the patient positively experiences: 1) discomfort and desire to move the extremities, 2) physical movement in an effort to relieve the discomfort, 3) the increase of symptoms at rest with temporary relief by movement, and 4) the symptoms worsening in the evening [8]. Others developed an algorithm for more clearly defining the diagnosis of RLS based on the Restless Legs Syndrome-Diagnostic Index (RLS-DI). The RLS-DI is a ten-part questionnaire that (a) supports the diagnosis of RLS (parts 1-4), (b) captures the frequency and occurrence of symptoms, and (c) excludes other causes of the sleep disorder [9]. The Cambridge-Hopkins Restless Legs Syndrome Diagnostic Questionnaire (CH-RLSDQ) represents another method of diagnosis for RLS, and it includes the basic diagnostic features of RLS as well as additional items for differential diagnosis of conditions that imitate symptoms of RLS, therefore further categorizing diagnosis as primary RLS [10]. Collectively, the diagnosis of RLS depends upon the initial four IRLSSG Diagnostic Criteria, with additional information captured on its qualitative experience and specificity. These methods allow for accurate identification of patients with a positive RLS diagnosis.

2.3. Measurement of RLS severity

The understanding and treatment of RLS further requires measurement of symptom severity and frequency. Symptom severity is most commonly quantified using the International Restless Legs Syndrome Study Group Rating Scale (IRLSSG Scale). The IRLSSG Scale contains 10 questions that generate a global score assessing the overall severity of symptoms as well as the frequency and impact of symptoms on daily life over a period of the previous seven days [8]. Overall severity scores are determined by summing the answers on the questionnaire for a maximum score of 40. For instance, item one inquires, “How you would rate the RLS discomfort in your legs or arms?,” with choices of very severe (4), severe (3), moderate (2), mild (1) or none (0). Item seven asks, “How often do you get RLS symptoms?,” ranging from (4) very severe (this means 6 to 7 days a week) to (1) mild (1 day a week or less), or (0) none. Total scores that range from 0-10 indicate mild symptoms, 11-20 moderate, 21-30 severe, and 31-40 indicate very severe symptoms [8]. The IRLSSG Scale allows physicians and researchers to measure the degree of symptoms and understand the factors and treatments that influence RLS.

2.4. Epidemiology

The lifetime prevalence of RLS ranges between 5 and 15 percent in the general population [11-15] with an annual incidence of approximately 1.7 percent [13]. There are various demographic factors influencing the prevalence of RLS. The prevalence of RLS significantly increases with age [12, 14, 16] and women have twice the risk compared with men [6, 12, 16-18]. This might be explained by a high prevalence of RLS during pregnancy [12, 19, 20]; RLS is the most common movement disorder among women during pregnancy with a reported prevalence of 26% [19]. There is a genetic component associated with idiopathic RLS suggesting hereditary involvement [17, 20]; those with one or more immediate family member diagnosed with RLS have a higher risk of developing RLS than individuals without a family history of RLS [20].

RLS may actually be under-diagnosed, as many people report experiencing symptoms, but a large portion of the population remains undiagnosed [11, 16, 18]. Although as many as 81% of people report having previously discussed symptoms with a primary care physician, only 21% were actually provided with a diagnosis from the physician [11]. This discrepancy in diagnosis of RLS can lead to a lack of effective treatment as well as a deficiency in the understanding of RLS and its many consequences.

2.5. Pathophysiology

The pathophysiology of RLS is not well understood. The syndrome has been associated with various clinical conditions that might shed light on its pathophysiology. Recently, an epidemiological review reported a prevalence of 11.1% to 25% in patient populations [17]. Of the patients with RLS, between 23% and 34% of these individuals present with iron dysregulation or uremia [19-25]. This may result in decreased brain iron concentration caused by low blood ferritin concentrations [26]. However, many individuals with RLS often have normal iron levels, suggesting an impairment of iron transportation into the brain [26, 27]. Some studies have reported a reduction in symptoms observed with iron repletion [24], yet this is not a consistent observation.

Dopamine dysregulation is a commonly reported theory for the pathophysiology of symptoms in RLS [27-29]. The positive responses observed in the symptoms of RLS with dopamine agonist treatment suggests that symptoms originate with a hyper-functional dopamine system [30]. Research in animal models indicates a dysfunction in the dopamine receptor gene in the diencephalon dopamine system [28], decreased binding potential for dopamine receptors and transporters [27], and dorsoposterior hypothalamic dopaminergic system suggesting spinal dopamine dysfunction [29]. These animal models further suggest that changes in dopamine regulation may be secondary to iron deficiency [30], indicating a possible iron-dopamine connection in the pathophysiology of RLS [21].

Other brain mechanisms are speculated to have some involvement in RLS pathology, including dysfunction in opioid regulation, the serotenergic or glutamatergic systems [30], impairment of the central somatosensory processing system [31], and inflammatory/immune changes [32]. Dysfunction in these neurological pathways associated with RLS could be related to other neurological disorders [1, 2, 4, 32-36], including spinal cord lesions [37, 38], Parkinson's disease [39], and multiple sclerosis [1, 2, 36, 37, 40].

2.6. Patient consequences

RLS is associated with a higher risk of experiencing a multitude of undesirable outcomes. Those with RLS are at a greater risk of insomnia [13, 41], excessive sleepiness [13], depression [30, 41], anxiety [41, 42], decreased quality of life [11, 12, 43] and general poorer health [16, 17] than those without the syndrome. The consequences accompanying RLS are often underestimated. Individuals with RLS often report experiencing poor sleep quality and severe sleep disturbances [16], leading to a greater risk of insomnia and increased daytime sleepiness [13]. Lack of sleep in individuals can have profound effects on daytime productivity. Approximately one day of work per 40-hour week is lost due to sleep problems associated with RLS [16] leading to a significant financial loss to the employer [43]. In combination, there is a higher prevalence of anxiety and emotional-oriented coping of stress [41, 42], as well as higher rates of depression in individuals with RLS compared to those without RLS [30, 41]. Collectively, individuals with RLS experience a significantly lower quality of life than those without RLS in both clinical conditions and the general population [12, 43, 44].

2.7. Burden of RLS in society

There is increasing recognition regarding the clinical and financial burden of RLS in society with physician visits, hospitalizations, and emergency room visits. Individuals with RLS experience a significant economic burden with an estimated total cost of $40,497 USD annually [45]. Approximately $30,297 USD is attributed to direct annual costs including emergency room visits, hospitalizations, and physician visits and $10,200 USD in indirect annual costs is attributed to absenteeism and presenteeism [45]. Healthcare resource costs (e.g., RLS-related practitioner and medical visits, specialist visits, emergency room visits, and treatments) significantly increase with symptom severity from $350.54 USD direct annual cost per patient with mild symptoms to an estimated cost of $490.70 USD per patient annually with severe symptoms [16]. In a matter of three months, approximately 57.6% of individuals visit a physician; 31.2% of visits were RLS-related, and 12.5% were RLS-related emergency room visits. A notable personal burden is placed on patients and family members as well as on society, suggesting an increasing need for proper diagnosis and safe, effective, and affordable treatment of RLS.

2.8. Management of RLS

The experience, prevalence, consequences, and burden of RLS present a strong case for its effective

management. The most common treatment of RLS involves pharmacological agents including dopamine agonists (carbidopa/levodopa or L-dopa), opioids, benzodiazepines, and anticonvulsants [6, 46-48]. Dopamine agonists are the most studied with the highest safety and efficacy for reducing symptoms [48-50]. Although pharmacological treatment reduces symptoms of RLS, there are numerous side effects associated with this treatment option, including nausea, dizziness, exacerbation of sleep apnea, headache, fatigue, and sleepiness [6, 46]. Accordingly, first line treatments with pharmacological options alone may not be the optimum management of RLS symptoms.

Other researchers have assessed non-pharmacological options for the treatment of RLS symptoms, including mental alerting activities, avoiding exacerbating substances (i.e. caffeine) or medications, treatment of iron deficiency, pneumatic compression, massage, near-infrared (NIR) light therapy, complementary and alternative medicine (i.e. vitamin supplementation), and physical activity [15, 48, 51]. In patients with low-normal ferritin, oral iron therapy has been efficacious for reducing symptoms [52, 53]. Pneumatic compression has led to a significant decrease in symptoms and may enhance venous and lymphatic drainage as well as significantly increase vascular blood flow [54, 55]. Massage therapy has decreased symptoms of RLS, theoretically due to the increased circulation, increase in blood dopamine or the tactile stimulation effects on the central nervous system [51]. Alternatively, researchers speculate that NIR light therapy elicits a reduction in symptoms due to the release of nitric oxide (NO) in the endothelium, similar to the release of NO during exercise [51, 56].

2.9. Exercise training in RLS

There is a growing interest and corpus of research on exercise as a behavioral approach for managing RLS and its consequences. This research has compared exercise with a control condition and exercise with pharmacological approaches for managing RLS symptom severity.

Exercise vs. Control. We located five studies evaluating RLS symptom changes in response to an exercise regimen (Table 1) [57-61]. All five studies demonstrated significant improvements in RLS symptom severity when compared to baseline or a control group at the end of each study. Two studies were conducted on otherwise healthy individuals, and three on uremic patients with reports of improvement from 38.9% to 57.9% reduction in symptom severity. Exercise protocols consisted of aerobic training on a cycle ergometer (4) or treadmill walking and strength training (1) with the stimulus ranging from light to moderate (4) or vigorous (1) intensity for 30-50 minutes, 3 days per week ranging for 12-24 weeks.

To date, the largest randomized controlled trial examined the effect of a 12 week exercise regimen on RLS symptoms in 23 patients with moderate to severe RLS [57]. The subjects were apparently healthy, other than symptoms of RLS, and were randomly assigned into control (n = 12) or exercise (n = 11) conditions. The exercise condition involved aerobic training at 40-60% age-predicted heart rate maximum on a treadmill, as well as lower-body resistance training at 60% 1-repetition maximum (1RM), three times a week for 12 weeks. The exercise condition was associated with a 39% decrease in RLS symptom severity from baseline to 6 weeks, and no significant change from 6 to 12 weeks [57].

Other studies reported complimentary improvements in overall functional capacity and sleep quality associated with chronic aerobic exercise in those with RLS. One study, conducted over a six-month period, had 12 participants complete 45 minutes of cycling at 60-65% maximal exercise capacity three times weekly. The researchers observed a significant 58% decrease in symptoms of RLS, as well as improved functional capacity, sleep quality, depression score and daytime sleepiness [59]. These findings suggest that a consistent exercise program can successfully promote a safe and effective reduction in RLS symptoms, as well as reduce the risk of various co-morbidities associated with RLS.

Exercise vs. pharmacological treatment. As discussed previously, first-line treatment options for RLS are generally pharmacological; however, there is reason to believe that exercise, alone or in combination with pharmacology, can be mutually beneficial at reducing symptoms, particularly if working through different mechanisms. One study compared the effects of exercise training alone to a combination of exercise training and low-dose dopamine agonist (DA) treatment [62].

Table 1. Studies conducted on the effects of exercise versus a control condition on the symptoms of RLS.

Study	Sample	Frequency	Intensity	Time	Type	Outcome measures	Key features	Results
Aukerman 2006 [57]	Exercise group (n = 11) Control (n = 12) Moderate to severe RLS	3 days per week for 12 weeks	40-60% HR max, 10-13 RPE and 60% of one-RM	30 minutes (with warm up and cool down)	Treadmill walking and lower body strength training	IRLSSG Scale; CHAMPS physical activity; at baseline, 6, and 12 weeks	Control group (Rest)	39% decrease in symptoms from baseline to 6 weeks; maintained from 6-12 weeks
Esteves 2011 [58]	Participants (n = 11) diagnosed by physician	3 times per week for 6 months	Max effort test (50-75% VO2 max)	50 minutes	Aerobic training on cycle ergometer	PSG (sleep parameters) IRLSSG scale at 12 and 24 weeks	Never received treatment for symptoms	Significant reduction in symptoms from baseline to 36 and 72
Giannaki 2013[59]	Uremic patients with RLS (n = 24) on dialysis, for RLS (Progressive exercise group vs. cycling with resistance)	3 times per week for 6 months	60-65% maximal exercise capacity	45 minutes during dialysis	Aerobic training on cycle ergometer	IRLSSG Scale; sleep quality; depression score; daily sleepiness scale (ESS)	Inactive and no previous treatment	57.9% decrease in symptoms, increased sleep quality and decreased depression compared to baseline; no differences in control group
Mortazavi 2013 [60]	26 patients with renal failure on dialysis	3 times a week for 16 weeks	Borg Scale of 10-12 (light-moderate)	30 minutes between 2 & 3 hours of dialysis	Aerobic training on cycle ergometer	IRLSSG Scale, Quality of Life (QoL) at baseline and 16 weeks	Randomly assigned to control or exercise	Significantly reduced symptoms in the exercise group compared to control. No significant changes in QoL
Sakkas 2008 [61]	14 patients on dialysis with RLS; Exercise group (n = 7), Control (n = 7)	3 times a week for 16 weeks	65-75% maximum power capacity	45 minutes between 2 & 3 hours of a 4-hour dialysis session	Aerobic training on cycle ergometer	IRLSSG: Quality of Life, ESS, Sleep diary, Depression Scale, functional testing	Chose to be in the exercise or control group	42% decrease in symptoms at 16 weeks. Increases of 25% in Quality of Life, 50% in sleep and 28% in functional capacity

Fourteen patients with uremic RLS on hemodialysis were randomly assigned to either the exercise and placebo group or the exercise and DA group. After 6 months of treatment, both groups demonstrated a significant decrease in symptoms by approximately 60% [62], but there were no differences between conditions. Another study compared exercise against dopamine agonists (DA) in patients with uremic RLS over a six-month period. Results demonstrated that exercise elicited a 46% decrease in symptoms and the dopamine agonist alone prompted a 54% decrease of symptoms [63]. These studies suggest that exercise can be considered a non-pharmacological treatment adjuvant for patients with RLS. The similar effect between exercise alone or exercise plus drug suggests similar mechanisms of action, such that exercise might reduce RLS through dopamine regulation.

3. Restless legs syndrome in multiple sclerosis

MS is a common, non-traumatic disabling neurological disease among young and middle-aged adults, and there is accumulating evidence for the prevalent and burdensome expression of RLS in MS [1, 3]. The presence of RLS seemingly is associated with decreased myelin integrity in the cervical spinal cord in MS [2], and RLS is associated with increasing levels of neurologic disability [1].

3.1. Prevalence

The prevalence of RLS is substantially higher in MS than the general population [1, 2, 36, 64]. One recent review reported that the prevalence varies between 13% and 65% of MS cases, but only between 2.8% and 18.3 of controls [1, 4]. There are known risk factors for RLS in MS, including older age, longer MS duration, higher global, pyramidal, and sensory disability, and the presence of leg jerks before sleep onset [1]. RLS is more prominent in primary progressive MS than relapsing-remitting MS [1, 36].

3.2. Burden

Sleep disorders are frequent problems of RLS in the MS population, and play an important role in the development of fatigue and other decreased functional outcomes [65]. Patients with MS and RLS report a higher rate of excessive daytime sleepiness [1, 66], increased sleep complaints (i.e., longer sleep latency, shorter total sleep time, and higher prevalence of insomnia), increased clinical disability [1, 67], and increased rate of depression and fatigue [67, 68]. We did not locate any studies assessing the cost associated with RLS in the MS population.

3.3. Treatment

To date, minimal research exists on how to manage RLS within the MS population, yet appropriate treatment of RLS in patients with MS may improve measures of fatigue and other clinical outcomes [69]. The recommended treatments are similar to those in the general population, and include iron supplementation for ferritin levels less than 50 ng/ml, reduction or discontinuation of medications and substances that exacerbate RLS, and the use of dopamine agonists, opioids, and anticonvulsants [70]. Although pharmacological treatment has been beneficial for those with RLS in the general population, many comorbidities and side effects exist in the MS population with the adherence to pharmacological treatment. Currently, there is a lack of research-based non-pharmacological treatment recommendations such as exercise training for patients with MS who have RLS.

4. Future research directions and conclusion

There is a limited body of research on RLS in persons with MS. This is surprising considering the prevalence of RLS in MS. To that end, there is considerable research necessary for examining modifiable and non-modifiable predictors of RLS onset and severity, and changes in RLS over time as MS progresses. We further need research on the latent causes of RLS in MS, and this might involve magnetic resonance imaging of motor pathways and spinal cord as well as electrophysiological studies of spinal cord-mediated processes in MS. We require comprehensive evidence on the personal and societal burden of MS, including the direct and indirect costs of MS. We require evidence on the consequences of RLS in MS, including effects on walking, cognition, symptoms of fatigue, anxiety, and depression, poor sleep, quality of life, and participation. Such evidence will better justify research on pharmacological and non-pharmacological rehabilitation approaches for managing RLS, and we believe that specific focus should be directed toward exercise training and RLS in MS, particularly considering its broad benefits in MS [71, 72]. Such a research agenda could benefit from a range of methodologies,

including qualitative, cross-sectional, prospective, and experimental designs. We believe the time is ripe for a focal and comprehensive research effort on RLS and MS!

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to report.

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