Restless leg syndrome: A Narrative Review

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Abstract

The restless leg syndrome is an idiopathic condition typically related to the scarcity of iron or end stage renal infection. It is a notable age-related neurological issue more prevalent among females. Pathophysiology and treatment/management can be approximately linked to the dopaminergic system and iron metabolism. Dopaminergic treatment mutually includes levodopa and dopamine agonists and is usually the first choice in the management of idiopathic Restless leg syndrome (RLS). Apart from medications, physical activity and exercise are compatible with non-pharmacological intervention for decrementing the rigor of RLS. Presently, there is a lack of understanding of this condition often leads to misdiagnosis or under diagnosis. The main objective of this paper is to review the literature about RLS and its veiled management.

Key words- Restless leg syndrome, iron deficiency, dopamine deficiency, physical activity

1. Introduction

Restless leg syndrome (RLS) is a disorder with an idiopathic etiology, usually related to an insufficiency of iron, pregnancy or end-stage renal infection. The condition is defined as an intricate disorder with a latent genetic or environmental factor or both [1]. It was first explained by Thomas Willis in 1685 [2]. Subsequently in 1945, "Ekbom" a Swedish neurologist, expounded this condition in a monograph wherein he identified an increased predominance of the inadequacy of iron among patients with RLS [3] [4].

RLS is a sensory- motor condition with strong involvement of sensory symptoms, attended with an inescapable compulsion to move the leg- either one or both legs, depending upon the severity of the condition. In the initial phase, it usually involves the legs. However, as the condition progresses, the compulsion to move the legs may extend to arms or other parts of the body (trunk, head)[5]. In some cases, pain may overshadow the condition and lead to misdiagnosis of the same as a chronic pain condition. The sensory symptoms are felt when the patient is awake in a sitting or lying position and even nocturnally. Walking, stretching or bending the legs can bring partial relief from discomfort and may alleviate the symptoms[6]. It is an age-related neurological disorder which afflicts people in their advancing years. Studies report greater predominance of RLS in females than in males. Some studies indicate its prevalence in children, too, suggesting that children between 2 and 13.9 years fulfilled the criteria for RLS [7]. A similar study conducted on men aged 18-64 years estimated its prevalence in this age group at 58% [8].

Restless leg syndrome should have an essential criterion fulfilled for the precise identification of the condition. This clinical diagnostic criterion was formulated by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995. Meanwhile, National Institutes of Health Conference, the members of the IRLSSG and authorities of epidemiology and scale design, analyzed and revised the same criterion for a

vivid development which further took place in May 2002. In addition to this, the criterion was separately reviewed and reported in 2003 by IRLSSG with the indexing of clinical presentation of the condition[6].

2. Pathophysiology

2.1. Influence of Iron

The intensity of this condition develops with a reduction in peripheral iron stores, but the patients usually have an adequate amount of serum ferritin. The predominance increases with iron deficiency and is nine times higher in iron deficient anemic individuals than the normal ones. In such cases of RLS, aggressive management for the insufficiency of iron could be effective in reducing the intensity of the condition. The pathophysiology of RLS seems to be lesser peripheral and has a greater correlation with CNS iron status[9]. The major biological anomaly for RLS is an insufficiency of iron in the brain. According to MRI findings of the substantia nigra and red nucleus in the brain, an insufficiency of iron was reported and to a minor intensity, the putamen and caudate showed insufficiency too. Similarly, recent works of the literature suggest the diminished iron content in the thalamus[9].

Adjustment in iron regulatory proteins shows a complex communication. There is an additional escalation of the presence of H-ferritin but not L-ferritin in the RLS brains. Both these precursors have different functions though H-ferritin enhances transportation and storage of iron. The literatures suggest that there is reduction in receptors (transferrin) in neuromelanin cells of the substantia nigra. Autopsy examination of motor cortex micro vessels show a reduced amount of iron regulatory protein-1 action with reduced iron consumption/storage proteins of transferrin receptor, transferrin, and H-ferritin but no modification in the iron export protein, ferroprotein. There is faulty transportation of iron into the brain, especially into neuromelanin cells of the substantia nigra. The deterioration of transportation of iron to the brain also is seen in choroid plexus. The epithelial cells display not only reduced iron and H-ferritin with higher insufficiency of iron, but also show higher mitochondrial ferritin signifying mitochondrial iron uptake. The escalating rise in mitochondrial ferritin can be seen in the cells of substantia nigra but not the putamen. In these cells, there is greater mitochondria and a thus greater rise in the requirement of iron[9].

2.2. Influence of Dopamine

In RLS with brain dopamine deficiency, Levodopa managed to show an instant management profit. In the beginning, CSF testing determined no significant changes amid RLS and regulations for major proteins connected to dopamine. Continuous testing of 3-orthymethyl dopamine (3-OMD) led to an increase in the CSF in 2-independent samples. The rise in both 3-OMD and homovanillic acid (HVA) is elucidated as a rise in tyrosine hydroxylase activity with an escalation in dopamine production. The PET and single photon emission computerized tomography denoted a greater reduction in striatal D2 receptors with a constant in return to rising synaptic dopamine. The fluoro-L-dopa(f-DOPA) analysis displayed a reduction in striatal f-DOPA uptake which exhibits a greater rise in dopamine production with no cell loss in RLS. Reduction in D2 receptors and dopamine transporter (DAT) was seen with methylphenidate binding in rodents with insufficiency of iron. Therefore, brain imaging studies also show a rise in striatal dopamine, rather than an expected reduction[9].

3. Clinical presentation/ Diagnostic features

Rapid diagnostic screening of RLS can be done based on validated IRLSSG criterion. These questions can be used to effectively screen many population with its 100% sensitivity and 96.8% specificity. Although,

the provisional diagnosis always need to be confirmed by the corresponding patient's history and characteristics with the IRLSSG diagnostic criterion following an exclusion of secondary conditions[10].

Table 1 Characteristics of RLS by IRLSSG consensus

Diagnostic characteristics

1. An eagerness to move the limbs generally combined with few determinable discomforts.
2. Motor restlessness (floor pacing, tossing or turning in bed)
3. Deterioration of symptoms at rest with a partial relief by activity
4. Deterioration of symptoms in the daytime or at midnight

Associated characteristics

5. Unintentional forceful movements during alert and unconscious (PLM)
6. Sleep disruption followed by its consequences
7. Performing neurological examination in emergent cases
8. Change in age of onset with usual chronic, liberal course
9. Repeating a genetic history of cases

The above mentioned characteristics were revised in accordance with a consensus conference on RLS diagnosis held May1-3, 2002 at the NIH [11]

3.1. Limb sensitivity

The sensory disturbances in the limb are generally known as paresthesia's or dysesthesias which indicate aberrant sensations. However, a few patients did not present with paresthesia's or dysesthesias. They relatively complained of discomfort and ineffable sensations in the extremities[12]

3.2. Motor restlessness

Motor restlessness is characterized by floor pacing, tossing and turning in bed. The patient complains of an urge to move the limbs and seeks for the movement to allay the difficulty in their legs. Motor restlessness is considered as involuntary because they get triggered by paresthesia's or dysesthesias[12].

3.3. Uncompromising nocturnal pain

It has been observed that the symptoms of RLS get severe in the evening or during nighttime and RLS is uncompromising on lying and sitting position during the day or even at night. Patients with progressive symptoms commonly present with a H/o previous nighttime aggravation and relief by activity. According to RLS study group, nocturnal aggravation in RLS is not because the patients are lying down more at night. Instead, it is attributable to the presence of an independent factor known as "circadian" factor. The improvement of symptoms during daytime gives an impression to develop whether patients are disturbed sleep or not, whether they are lethargic or not[12].

4. Associated disorders

RLS can coexist with a lot of conditions such as *End stage renal failure* (ERSD). Its prevalence ranges from 6.6 to 8.3%. The surprising fact is that none of the pieces of literature discusses the correlation of the important factor, namely, "dialysis" to the occurrence of RLS in ERSD. A few studies suggest that RLS could be treated or ameliorated in patients after renal transplantation[7]. Another important co-morbidity

found to be correlated to RLS is *Parkinson's disease*. RLS and Parkinson's disease both have a similar pathophysiological mechanism as both rely on dopaminergic management. Nevertheless, dopaminergic pathways involved in both the disorders are independent as expected. Recent studies carried out using the IRLSSG criterion, show a greater predominance of RLS in PD patients[7]. *Stroke* is a condition which has been seen to activate RLS because of the same locations of lesions such as Basal ganglia (30%) and Pons (22%) [13]. *Sleep disorders or Insomnia* is also associated with RLS. Patients having sleep disorders are usually not able to sleep or stay awake or tend to wake up too early in the morning, feel drowsy after sleep or are lethargic and unable to concentrate the entire day. Sleep disturbances can lead to mood swings and distress due to which patients with RLS often seek help[14].

Patients with RLS have an increased prevalence of *depression and anxiety*. In a few studies, RLS has been correlated with *hypertension, cardiovascular disease (CVD)* and *cerebrovascular disease*. Patients who face altered sleep patterns because of RLS are prone to hypertension and CVD[14].In 1945, it was proposed that RLS is correlated with *pregnancy*. A study carried out on 500 pregnant women showed a prevalence of 19%. Similarly, a questionnaire distributed among 16,528 pregnant women in Japan to predict the prevalence of RLS showed an identical result of 19%[7]. There are a few other morbidities which can be associated or can coexist with RLS like Diabetes, Rheumatoid Arthritis, Fibromyalgia, Spinal nerve root irritation, Spinocerebellar ataxia (particularly SCA 3) and Marie-Tooth disease (type 2) but they need to be studied more to firm up their correlation with RLS.

5. Differential diagnosis [5]

RLS diagnosis should always be followed by excluding other diagnosis. The following are the common differential diagnosis that should be considered while assessing the patient with RLS.

1) Periodic limb movement disorder (PLMD)
2) Myelopathy, radiculopathy
3) Nocturnal leg cramps
4) Painful peripheral neuropathy
5) Hypotensive akathisia
6) Arthritis, lower limb
7) Volitional movements, foot tapping, leg rocking
8) Positional discomfort
9) Neuroleptic-induced akathisia
10) Painful legs and moving toes
11) Congestive heart failure
12) Vascular claudication, neurogenic claudication

5. Physiotherapy Management

5.1. Aerobic exercise

Signs of RLS inevitably improved during aerobic exercise. Aerobic exercise is productive in improving the severity of RLS symptoms in patients with chronic hemodialysis. Sakkas [15] recommended aerobic exercise as a suitable treatment for patients undergoing chronic hemodialysis. His study also suggested an

improvement in QOL of RLS patients during weeks of exercise. Therefore, aerobic exercise is useful in improving the sign of RLS for patients with chronic hemodialysis [15].

5.2. Targeted pressure on Muscles

Targeted pressure on muscles like abductor hallucis and flexor hallucis brevis muscles have proven to reduce the symptoms. The study found that it was nearly two times as efficacious as remarkable placebo treatment and 1.4 times as persuasive as ropinirole in decreasing IRLSSG scores, with nil side effects correlated with current medications for RLS [16].

5.3. Traction straight leg raise

Symptoms decrease on a subsequent course of traction in patients with a primary diagnosis of idiopathic RLS. This mobilization technique may influence central and peripheral neural pathways and alleviate RLS symptoms[17].

5.4. Near Infrared Light (NIR)

NIR may be a productive nonpharmacological management option for those patients suffering from RLS. Research suggests that the application of NIR light to the lower extremities of patients may alleviate the symptoms (as measured by IRLSRS) correlated with the condition[18].

5.5. Local and whole-body cryotherapy

Literature suggests that local and whole-body cryotherapy helps in alleviating RLS symptoms, QOL and sleep quality. Some evidence supporting the efficacy of local cryotherapy (at -17˚C) in alleviating RLS symptoms was also found. However, advancement was less distinct in the severity of symptoms, sleep quality and QOL in comparison to whole body cryotherapy at -60˚C[19].

5.6. Physical Activity/Exercise

Physical activity vital in improving strength and cardiovascular health of patients. Some authors have found that exercise performance can help decrease the risk of co-morbid conditions, which act as risk factors for RLS. Others suggest that exercise has an impact on RLS patients by improving circulation and release of endorphins, which improve mood and pain. Treadmill walking for thirty minutes at 60% heart rate max along with low intensity leg strength training for 12 weeks has been found to be effective for most patients[20].

5.7. Cognitive behavioral therapy (CBT)

Hornyak [20] showed coping strategies and quality of life of RLS patients with an acceptance based mindfulness approach. In this study, 25 patients of RLS received 90-min sessions of therapy. QOL was found to have become better and subjective symptom severity lessened[20].

6. Conclusion

There are various conditions that are baffled with RLS. Due to lack of better understanding of this condition, it is often unrecognized or misdiagnosed. Presently, the urge to write this paper was to expand knowledge and increase publicity about the condition and its underlying management. Apart from misdiagnosis, there are several myths and misconceptions such as “There is no good treatment for RLS”, which undoubtedly

lead to a depressing situation. Lack of awareness has often resulted in misdiagnosing RLS as muscle cramps and in consequence, its line of management taking a totally wrong direction. This is the right time to understand that RLS is a common and important condition which can cause serious distress to sufferers. Accurately diagnosing the underlying condition can improve the symptoms and even treat it.

Apart from medications, there is some evidence which supports nonpharmacological interventions such as exercise which may include aerobics, cryotherapy and even Yoga which may alleviate symptoms and decrease its severity. These forms of physical activities are highly sought because it enhances mind–set and agony by improving mood and reducing anxiety. It also decreases blood pressure, induces muscle unwinding, plays a critical role in improving sleep quality, general strength, and cardiovascular health of patients.

Conflict of Interest

The authors have no actual or potential conflicts of Interest.

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