A Review on management of Restless Leg Syndrome

Anuba P A[1], Swetha B[1], Arun G R[1], Shini Rubina S K[1], Sangeetha S[1], Sarumathy S[1*], Nanda Kumar R[2]

1. Department of Pharmacy Practice, SRM College of Pharmacy, Faculty of Medical & Health Sciences, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur, 603203, Chengalpattu (DT) -60203, Tamilnadu, India.

2.Department of General Medicine, SRM Medical College Hospital And Research Centre, Faculty of Medicine and Health Sciences, SRMIST, Kattankulathur, Chengalpattu (DT)-60203, Tamilnadu, India.

***Dr.Sarumathy S., M. Pharm., PhD.,**
Associate Professor,
Department of Pharmacy Practice,
SRM College of Pharmacy,
Faculty of Medical & Health Sciences
SRM Institute of Science and Technology,
SRM Nagar, Kattankulathur, 603203,
Chengalpattu (DT), TN, India.
Fax No.:044- 27453903, Tel No.: 044- 27417777
***Email: saruprabakar@gmail.com**
swetha12032000@gmail.com
arun26101999@gmail.com
at7122@srmist.edu.in

ABSTRACT

RLS (Restless Legs Syndrome) is one of the frequent illnesses that goes undetected or un diagnosed. According to reports, the incidence of RLS in India is far lower compared to the Western countries. RLS is a genetically driven organic neurological disorder whose iron metabolism is affected. RLS patients commonly experience a strong need to move as well as experience anxiety.The symptoms of restless legs syndrome include odd sensations in the legs, such as tingling, crawling, pulling, aching. The illness can also affect other body parts, such as the head, chest, or arms. Both sides of the body experience the feelings more frequently. They may exclusively occur on one side, or they may begin on one side before moving to the other. There are no proper management strategies available to treat RLS treatment.Opioids, benzodiazepines, anticonvulsants, Dopaminergic medicines, adrenergic pharmaceuticals, magnesium, iron and a wide selection of other substances are currently available for symptomatic management.

Key words: Restless Legs Syndrome, Diseases, Neurological Disorders, Neurotransmitter and metabolism, Diagnosis, Treatment.

DOINumber:10.14704/nq.2022.20.8.NQ44060 **NeuroQuantology2022;20(8):534-541**

INTRODUCTION

Restless Legs Syndrome (RLS) is a syndrome marked by unpleasant sensibility in leg such as burning, tugging, and stretching, which feel like "insects creeping within the legs," stated by National Institute of Neurological Disorders and Stroke (NINDS).[1] The earliest clinical report of RLS was published in the 17th century by physician who is also a British anatomist named Thomas Willis.[2] Ekbom, a Swedish neurologist, gave an extensive detail on disease in 1945.[3] It's now thought to be a genetically occurring neurological disease condition characterized by dopaminergic neurotransmitter dysfunction, which is directly impacted by iron metabolism.[4]

EPIDEMIOLOGY

The predominance of RLS in the normal community is expected to be between 5 and 10%, based on diagnostic manual and the age of the research population. Females are more prevalent than males, and the incidence increases as one gets older.[5] The Indian perspective on RLS is considered as an illness that is under-researched and possibly under-diagnosed,[6] Because there isn't much literature on restless leg syndrome in India, the actual prevalence is unknown. In the Indian literature, only hospital-based data was published, and no population-based surveys on restless legs syndrome were performed. According to a study, the incidence of restless legs syndrome in healthy people is 6.25 percent, but it is 34.37 percent in anaemic people.[7] Chronic menorrhagia and multiple blood donations (5times) were found to have strong link to an elevated threat of RLS, based on some studies. RLS seems to have a significant influence on sleep and is among the most bothersome conditions faced byhemodialysis patients.[8] In two investigations, The incidence of RLS was observed to be approximately 1 to 6 percent in patients with chronic kidney disease compared to none in normal individuals, and around 9 percent Among patients with sleep problems, with a 7:1 male-to-female ratio.[8-9] In contrast to western studies, this male predominance is most likely owing to symptomatic females under-reporting to hospitals.[10]

AETIOLOGY

RLS categorized as either idiopathic or can be secondary to chronic disease. Secondary RLS can occur in 25-30% of persons with iron deficiency disorders, such as renal failure, pregnancy and anemia.[11] Ekbom, one who recognized a family component in primary RLS. However intermittent or more symptomatic forms cannot easily be distinguished from family kinds, it is shown that individuals with hereditary RLS3 have an earlier beginning of RLS and a significantly more frequent deterioration throughout pregnancy. A minimum of 60% of individual impacted with idiopathic RLS have a favourable family history, according to clinical surveys.[12-13] In families with an average onset of symptoms of age 30 years or less is their substantial indications for autosomal dominant pattern of inheritance mediated by a single significant gene.[14] Symptoms and signs in majority of RLS patients in search of medical assistance will explain a strong desire to move as well as unpleasant sensations. It includes wide spectrum of symptoms in the legs, including tugging, burning and tightening, as well as the sensation of "insects crawling within the legs," that are usually sensory. These sensations are not unpleasant, but they are upsetting.[15] The sensations are usually described by the patient as unpleasant and well within leg, apart from on the surface.[15]

Regardless of its name, RLS symptoms can also impact over arms and other regions of the body. These other body parts may get involved in worsening condition of RLS, however the legs are afflicted initially and it is more severe than other parts of body. Rest or inactivity initiates or worsens the unpleasant sensibility.[16] More the relaxing posture lasts, more probable the symptoms may appear. A small percentage of patients experience involuntary spasmodic jerks of the legs rather than unpleasant sensations (RLS with a motor feature). Dyskinesia while awake (DWA) or periodic leg movements while awake (PLMW) are other names for these kind ofjerks, They may afflict one limb or the entire body, and they may show up when standing but subside while walking.

The slowing of cerebral cortical activity has been linked to the motor symptoms of RLS. During the illness's early stages, relief from unpleasant sensibility seen as soon as the activity starts, the effect may last throughout the duration of the activity.[17] Similar alleviation may be obtained by Anti-stimulation techniques, such as massaging the legs. Temperature variation is used as a coping mechanism by up to 82 percent of patients (e.g., taking hot or cold baths).[18] As the degree of RLS worsens, less alleviation is provided by frequent movements. Although persons with serious RLS may experience symptoms that persist throughout the day with symptoms more likely to be worsen in the evening or at night. It's been proven that the peak of RLS restlessness occurs in the hours following midnight which was demonstrated by utilizing polysomnography a technique for EEG determination of sleep as well as leg movements. [19]

DIAGNOSIS

The international RLS study group established and recently revised diagnostic criteria International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria for clinical evaluation of RLS. RLS16 must meet four essential criteria in order to be diagnosed. These are some of them: Occurrence of paraesthesia or spontaneous twitches in legs, or less frequently in other region of the body, cause an unpleasant desire to move the limbs, symptoms may become worse at rest or in the evening or during night with temporary or short lived relief by motor activity. Beneficial family history, positive effects of dopaminergic treatment, at least at the start of treatment, as well as periodic leg twitches when sleeping all help to confirm the diagnosis. The syndrome's associated features include disease progression based on the patient's age of onset and/or sleep disruption in the patient, which provide a prevalent morbidity for RLS and warrants specific attention in therapeutic decisions, and it is frequently examined as the primary reason for the patient attempt to medical assistance except for disorders that are secondary or being co-morbid causes for RLS, The examination carried out by the doctor is typically normal and are not aid in the diagnosis. Iron deficiency is a known risk factor that can be easily handled, therefore it's important to check your iron status on a regular basis. It's also a good idea to check for peripheral neuropathy and radiculopathy.

LABORATORY DIAGNOSIS

PLMS (periodic leg movements in sleep) are found to be more than 80% of all patients, these are uncontrollable leg jerks that occur at repeated intervals of 15 to 40 seconds after the onset of sleep. The frequency of periodic leg motions per hour of sleep (PLMS-index) is frequently employed as an objective indicator of RLS severity, with values greater than 5/hour deemed abnormal.[20]

Furthermore,PLMS index greater than 5/hour are seen in patients with sleep apnea syndrome, narcolepsy, or REM sleep behaviour disorder, emphasizing thepoor diagnostic findings.The serum ferritin content, and the standard anemia markers such as red blood cell count, hemoglobin, and hematocrit, should be measured as part of the patient examination for RLS. Adult ferritin levels should be between 20 and 300 mg/L for men and 20 to 150 mg/L for women.[21]

TREATMENT

RLS is treated symptomatically rather than curatively.[15] Reducing symptoms, their severity, and nighttime awakenings are the goal of therapy. Another major goal is to improve quality of life, which includes increasing general happiness, reducing daytime somnolence, and enhancing sleep quality.[21] These objectives are achieved by Non-pharmacological and pharmacological therapy

Non-pharmacological Management

No systematic trials for non-pharmacological therapy for RLS patients have been conducted. a wide range of experts recommend practicing good sleep habits, such as getting up and get into bed around the same hour every day. [22-23] Avoiding alcohol, coffee, and nicotine may help to alleviate symptoms. Hot baths, massages, stretching, and mild exercise are also recommended.[22] For evening symptoms, Mind-stimulating activities, such as word puzzles and video games, lessens symptoms and may be

beneficial. [24] The treatment for secondary RLS must be etiologic (for example: End-stage renal illness necessitates kidney transplantation).[25]

Pharmacological therapies

There is a scarcity of information on how to treat RLS. Several chemicals are currently accessible for pharmacological treatment, including dopaminergic medications, opioids, benzodiazepines, anticonvulsants, iron, adenosine, adrenergic medicines, magnesium, and others.

Iron supplementation

If ferritin values are less than 50 mg/L, most experts prescribe iron supplementation.[24-26] because patients may have symptoms when ferritin levels are below normal range. Iron supplementation hasn't been shown to help RLS sufferers who don't have a true iron shortage.[27]

Dopaminergic agents

A dopamine agonist, L-Dopa is the first-line choice of treatment for RLS.[4]In mild and intermittent RLS, L-DOPA combined with bestride or carbidopa (dopa-decarboxylase inhibitors) is recommended. The dopa-decarboxylase component prevents levodopa from being converted to dopamine in the peripheral nervous system. As a result, more levodopa can penetrate the blood–brain barrier. L-DOPA has a starting dose of 50-62 mg[5] and a final dosage of 100-250 mg. [4] Nausea, headaches, altered taste sensations, and dry mouth are all common side effects of levodopa.[28-29] Because levodopa is taken in modest doses, RLS does not cause dyskinesias like Parkinson's disease does.[30] Rebound and augmentation found to be two therapeutic issues particular to RLS. The reappearance of symptoms after medication wears off is known as rebound, and it is directly proportional to the medication's half-life.[25] This side effect affects 20 to 35 percent of levodopa users.[24]

Dopamine agonists

Pergolide, pramipexole, and ropinirol are dopamine agonists that have been widely utilized in RLS. [31] Piribedil is a dopamine agonist that has been used to treat RLS in the past. [15] These drugs bind to D2 and D3 striatal DA(dopamine receptors) receptors, Pramipexole, on the other hand, has a far stronger affinity towards D3 –receptor than the D2 –receptor. Such drugs have greater half-life than levodopa., which eliminates worries about the short-term impacts during the sleeping period. While dopamine agonists are less likely than levodopa to cause augmentation, or it nevertheless happens. RLS has also been examined with cabergoline and rotigotine.[31]

Ropinirole is the first drug to be licenced by the US Food and Drug Administration (FDA) for the treatment of RLS. The initial dose is 0.25mg, with the final dose ranging from 0.5 to 4.0mg. It has less gastrointestinal adverse effects and is better tolerated. Headache (34.4 percent), nausea (31.3 percent), dizziness (18.8%), and somnolence are the most prevalent side effects (15.6 percent). In 12.5 percent of ropinirol-treated individuals, augmentation was observed.[21]

Oral pergolide also been used efficiently to treat RLS patients. The initial dose is 0.025mg, with a final dose of 0.5-1.0mg. Insomnia, dyspepsia, nausea, headache, and rhinitis are some of the side effects.[32] Peroxide-treated patients are shown to have augmentation in 15-27 percent of cases.[33-34]

Piribedil has reported to be beneficial in the treatment of RLS. It is used in doses ranging from 25 to 350 mg. The phenomena of augmentation have not been evidenced. Sleepiness, mental fogging, chest pain, and palpitations have all been mentioned as side effects. Piribedil has been considered as a first-line medication for the treatment of RLS.[4]

Anticonvulsants

For the treatment of RLS, several oral anticonvulsants have been tried., but gabapentin, carbamazepine, and valproic acid are three drugs that have evidence from placebo-controlled studies. All three drugs increase the amount of -amino butyric acid (GABA), which may impede impulse in the spinal cord transmission. GABA may also contribute an important role in the release of dopamine and serotonin, which could have an impact on RLS in unknown ways.[35-37] Gabapentin has been suggested as a first-line treatment for uncomfortable RLS caused by polyneuropathy. Gabapentin has a starting

dose of 300 mg and a maximum dose of 1,500-3,000 mg. Carbamazepine is normally begun at 50 mg and gradually increased to 100-400 mg. Sleepiness, dizziness, and exanthema are the most prevalent side effects. Valproic acid has a starting dose of 300 mg and a maximum dose of 1,000 to 3,000 mg. Increased body weight, tremor, weariness, and hair loss are all common side effects of valproic acid.[4]

Opioids and opioid-agonists

Opioids are commonly used to treat RLS, however there is little evidence to back up their usefulness. Propoxyphene and oxycodone are the only agents studied in limited, controlled trials. [21] Both the drugs reduce PLMS related to excitement. Tramadol was tested in a study and was found to be more efficient than earlier therapies by patients.[38] Opioids' use in the treatment of RLS is limited due to side effects and addiction. Propoxyphene 400-600 mg; codeine 30-180 mg; tramadol 50-300 mg; oxycodone 20-30 mg; and morphine 30-45mg are the opioid doses used.

Benzodiazepines

Clonazepam is the most commonly researched benzodiazepine for RLS among the benzodiazepines.[21] Clonazepam's initial dose is 0.25mg, while the conclusive dose range is 1.0-2.0mg.[4] Other benzodiazepines used include zolpidem (dose range: 5.0mg starting dose to 10-20mg final dose) and zaleplon (dose range: 5.0mg initial dose to 10-20mg final dosage). Senior persons experience nightfall, a hangover the next day, and habituation are all side effects of benzodiazepines.[4]

CONCLUSION

RLS is often referred to as one of the most underdiagnosed disorders. Because there is no consensus on the appropriate treatment for RLS, it is confounded by the wide variety of therapeutic choices available. The most extensively researched medications for the treatment of RLS are dopaminergic drugs. Anticonvulsants, iron, opioids, and benzodiazepines are among the other medications. Gabapentin and L-dopa appear to be the best treatments for RLS sufferers. Pergolides and Pramipexole caused amplification as well as severe side effects, but opioids induced tolerance, addiction, and intense side effects, therefore it should only be used as a last resort. Due to the lack of enhancement phenomenon, the first-line medication for RLS treatment is indicated to be piribedil in a recent trial.

FUNDING

None

CONFLICT OF INTEREST

The authors declare no competing interests.

REFERENCES

[1]. Rados C. Treating restless legs syndrome. FDA Consum. 2006;40(3):26-9. PMID 16906664.

[2]. Willis T. De anima brutorum. London: Wells and Scot; 1672.

[3]. Ekbom K. Restless legs: a clinical study. Acta Med Scand. 1945;158;Suppl:1-123.

[4]. Mathis J. Update on restless legs. Swiss Med Wkly. 2005;135(47-48):687-96. doi: 2005/47/smw-11163, PMID 16511704.

[5]. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med. 2004;5(3):237-46. doi: 10.1016/j.sleep.2004.03.006, PMID 15165529.

[6]. Bhowmik D, Bhatia M, Tiwari S, Mahajan S, Gupta S, Agarwal SK, Dash SC. Low prevalence of restless legs syndrome in patients with advanced chronic renal failure in the Indian population: a case controlled study. Ren Fail. 2004;26(1):69-72. doi: 10.1081/jdi-120028557, PMID 15083925.

[7]. Rangarajan S, D'Souza GA. Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital. Sleep Med. 2007;8(3):247-51. doi: 10.1016/j.sleep.2006.10.004, PMID 17368978.

[8]. Kutlu R, Selcuk NY, Sayin S, Kal O. Restless legs syndrome and quality of life in chronic hemodialysis patients. Nigerian journal of clinical practice [Internet]. 2018 May 1 [cited 2022 Jan 12];21(5):573–7. doi: 10.4103/njcp.njcp_84_17, PMID 29735856

[9]. Bhowmik D, Bhatia M, Gupta S, Agarwal SK, Tiwari SC, Dash SC. Restless legs syndrome in hemodialysis patients in India: a case controlled study. Sleep Med. 2003;4(2):143-6. doi: 10.1016/s1389-9457(03)00005-4, PMID 14592345.

[10]. Kumar VG, Bhatia M, Tripathi M, Srivastava AK, Jain S. Restless legs syndrome: diagnosis and treatment. J Assoc Physicians India. 2003;51:782-3. PMID 14651138.

[11]. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep. 1998;21(4):371-7. doi: 10.1093/sleep/21.4.381, PMID 9646381.

[12]. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with newstandard criteria. Mov Disord. 1997;12(1):61-5.doi: 10.1002/mds.870120111, PMID 8990055.

[13]. Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology. 1996;47(6):1435-41. doi: 10.1212/wnl.47.6.1435, PMID 8960723.

[14]. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, Strohle A, Eisensehr I, Dichgans M, Gasser T, Trenkwalder C. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol. 2002;52(3):297-302. doi: 10.1002/ana.10282, PMID 12205641.

[15]. Spolador T, Allis JC, Pondé MP. Treatment of restless legs syndrome. Braz J Psychiatry. 2006;28(4):308-15. doi: 10.1590/S1516-44462006000400012. PMID 17242812.

[16]. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health, International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101-19. doi: 10.1016/s1389-9457(03)00010-8, PMID 14592341.

[17]. Montplaisir J, Lapierre O, Lavigne G. The restless leg syndrome: a condition associated with periodic or aperiodic slowing of the EEG. Neurophysiol Clin1994; 24:131-40. doi: 10.1016/s0987-7053(94)80003-0, PMID 8202059.

[18]. Winkelmann J, Wetter TC, Collado-Seidel V et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep2000; 23:597-602. PMID 10947027.

[19]. Hening WA, Walters AS, Wagner M et al. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. Sleep1999; 22: 901-12. doi:10.1093/sleep/22.7.901, PMID 10566908.

[20]. Coleman RM, Pollack CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders.Ann Neurol1980; 8:416-21. doi: 10.1002/ana.410080413, PMID 7436384.

[21]. Ryan M, Slevin JT. Restless Legs Syndrome. Am J Health-Syst Pharm 2006; 63 (17): 1599-1612.

[22]. Parker KP, Rye DB. Restless legs syndrome and periodic limb movement disorder. Nurs Clin North Am 2002; 37:655-73. doi: 10.1016/s0029-6465(02)00031-2, PMID12587366.

[23]. Hening W, Allen R, Earley C et al. The treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999; 22: 970-99. PMID 10566916

[24]. Silber MH, Ehrenberg BL, Allen RP et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004; 79: 916-22. doi: 10.4065/79.7.916, PMID 15244390

[25]. Walther BW. Treating restless legs syndrome: current pathophysiological concepts and clinical trials. Expert OpinInvestig Drugs2002; 11 (4): 501-14. doi:10.1517/13543784.11.4.501, PMID 11922859.

[26]. Avecillas JF, Golish JA, Giannini C, Yataco JC. Restless legs syndrome: keys to recognition and treatment. Cleve Clin J Med2005; 72: 769-76. doi: 10.3949/ccjm.72.9.769, PMID 16193825.

[27]. Davis BJ, Rajput A, Aul EA, Eichhorn GR. A randomised,double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol2000; 43: 70-5. doi:10.1159/000008138, PMID 10686463.

[28]. Trenkwalder C, Stiasny K, Pollmacher T et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a doubleblind, crossover trial. Sleep1995; 18: 681-8. doi: 10.1093/sleep/18.8.681, PMID 8560135.

[29]. Benes H, Kurella B, Kummer J et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind,randomised, multicenter, crossover trial. Sleep1999; 22:1073-81. doi: 10.1093/sleep/22.8.1073, PMID 10617168.

[30]. Schapira AH. Restless legs syndrome: an update on treatment options. Drugs2004; 64:149-8. doi: 10.2165/00003495-200464020-00003, PMID 14717617.

[31]. Foley P, Gerlach M, Double KL, Riederer P. Dopamine receptor agonists in the therapy of Parkinson's disease. J Neural Transm2004; 111: 1375-446.doi: 10.1007/s00702-003-0059-x, PMID 15480844.

[32]. Wetter TC, Stiasny K, Winkelmann J et al. A randomized controlled study of pergolide in patients with restless legs syndrome. Neurology1999; 52: 944-50. doi: 10.1212/wnl.52.5.944, PMID 10102410.

[33]. Earley CJ, Yaffee JB, Allen RP. Randomised, double-blind,placebo-controlled trial of pergolide in restless legs syndrome. Neurology1998; 51: 1599-602. doi: 10.1212/wnl.51.6.1599, PMID 9855508.

[34]. Silber MH, Shepard JW, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study.Sleep1997; 20: 878-82. doi: 10.1093/sleep/20.10.878,PMID 9415948.

[35]. Garcia-Borreguero D, Larrosa O, de la Llave Y et al. Treatment of restless legs syndrome with gabapentin: a double-blind,cross-over study. Neurology2002; 59: 1573-9.doi: 10.1212/wnl.59.10.1573, PMID 12451200.

[36]. Zucconi M, Coccagna G, Petronelli R et al. Nocturnal myoclonus in restless legs syndrome: effect of carbamazepine treatment. Funct Neurol1989; 4: 263-71. PMID 2507405.

[37]. Eisensehr I, Ehrenberg BL, Rogge Solti S, Noachtar S. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid: a randomized, placebo-controlled,double-blind, cross-over study. J Neurol2004; 251: 579-83. doi: 10.1007/s00415-004-0367-6, PMID 15164191.

[38]. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry 1999; 60: 241-4.doi: 10.4088/jcp.v60n0407, PMID 10221285