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A Review on Restless Legs Syndrome and its Management

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Abstract
Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a neurological sensorimotor disorder which is characterized by uncontrollable urge to move legs which is accompanied by painful sensation. RLS can be distinguished into primary (idiopathic) and secondary forms. Prevalence of RLS is around 1-15 % worldwide. Prevalence of RLS appears more in Northern and Western European countries and less common in Asian and South European countries. In South-India, prevalence of RLS is 2.1 %. Symptoms may appear during periods of rest and inactivity at evening-night times and relieved by movement. Symptoms of RLS include uncontrollable urge to move legs, uneasiness and discomfort in legs. Symptoms get worse during late evening and night (bedtime). RLS is commonly seen in pregnancy (secondary RLS) and prevalence is ranged between 10-34%. Dopaminergic neuron system and iron status is mostly involved in the pathophysiology of RLS. Drugs used in treatment of RLS include dopaminergic agents (ergot and non-ergot derivatives), benzodiazepines, anti epileptic agents, opioids and iron supplements. Ropinirole and rotigotine transdermal patch are highly effective in treatment of RLS.
Keywords: *Restless legs syndrome, Dopaminergic agents, Ropinirole, Rotigotine, Iron, Non-pharmacological treatment.*

Introduction

Restless Legs Syndrome (RLS) is a common movement disorder characterized by uncontrollable urge to move the legs, which is accompanied by unpleasant or painful sensations in legs. These sensations appear or worsen during rest and at bedtime, especially in the evening-night and relieved by regular motor activities[1, 2]. RLS is most frequently associated with disturbed sleep due to which the patient may experience changes in onset of sleep, delayed sleep and difficulty in maintaining sleep pattern[3]. The prevalence of RLS in general population is 2-15%[4]. RLS is a neurological disorder that can cause daytime sleepiness, tiredness, which can affect mood, concentration, regular activities, routine work, emotions and personal relationships. RLS patients more commonly report that they are unable to concentrate, have impaired memory and failed to complete daily tasks. Symptoms most commonly seen in RLS are unpleasant sensations like

parasthesia/ dysesthesia in legs, painful sensation in legs, discomfort and uneasiness[5]. RLS patients obtain relief from symptoms with movement of legs; although the relief is temporary and symptoms may return rapidly[3].

Prevalence

The prevalence of RLS is 2-15% in general population[4]. Incidences are more with positive family history and genetics. RLS in women is twice than men. Prevalence of RLS among Whites is 5-15%[2]. RLS appears to be more common in Northern and Western European countries and less common in Asian and southern European countries (Turkey)[3]. In South-India, the prevalence of RLS is shown to be 2.1%[7]. The prevalence of RLS is ranged from 10-34% in pregnancy condition[10].

Table-1 Prevalenceof RLS in Different Countries [6,7,11,12]

S.no	Country	Prevalence (%)
1	Canada	10-15%
2	United States	10%
3	South Korea	7.9%
4	Netherlands	6.0%
6	UK	4.6%
7	Ireland	4.6%
8	Spain	4.6%
9	Denmark	3.5%
10	Turkey	3.4%
11	Australia	2.5%
12	Germany	2.5%
13	South India	2.1%

Etiology

RLS is categorized under two factors i.e, primary and secondary factors[1]. Primary RLS represents a familial disorder. Secondary RLS occurs due to other pathological conditions like peripheral neuropathy, end stage renal disease, iron deficiency, pregnancy, myelopathies, rheumatoid arthritis, Parkinson's disease and Attention-Deficit Hyperactivity Disorder in children[9,13]. The other possible secondary factors include deficiency of folate/ B_{12}/ magnesium, alcohol abuse, idiopathic neuropathy, caffeine, Chronic Obstructive Pulmonary Disorder, hypothyroidism and hyperthyroidism[5]. In general, if the onset of symptoms is seen after age 45, it should be suspected as secondary RLS[9]. Evidence has shown that decreased levels of iron/ ferritin and dopamine are responsible for RLS[8]. Other etiologies of RLS include dysfunction of the endogenous opioid and dopaminergic systems[13].

Genetics

RLS is a familial disorder. Primary RLS commonly run in families mostly about 60%[14,15]. The genetics of RLS is shown unclear and it is rather considered to be complex and heterogenetic disorder[3]. Six different genes with single nucleotide polymorphisms has been identified by GWAS and they include BTBD9 (chromosome 6p21.2), MEIS1 (chromosome 2p14), PTPRD (chromosome 9p24.1-p23), MAP2K5 (chromosome 15q23), SKOR1 (chromosome 16q12.1) and TOX3 [14,15].

Clinical Features

The symptoms of RLS include uncontrollable urge to move legs, painful sensation and unpleasant sensations [1, 2]. Other symptoms which are often seen in RLS patients include uneasiness in legs, nervousness, discomfort in limbs (crawling, itching, burning, tingling and pricking sensations) and leg cramps [5]. These features are most commonly seen when in rest and inactivity conditions during evening- night times and are relieved by motor activities (stretching / moving of legs)[5]. Symptoms get worse during late evening and at bedtime[5]. As the duration of disease prolongs, the RLS may affect arms[6]. Poor sleep quality and depression are the conditions associated with sympathetic-parasympathetic imbalances[17].

Pathophysiology

In the pathophysiology, the role of iron and dopaminergic neurons is more involved. During MRI studies, neuropathological specimens, brain imaging, cerebrospinal fluid evaluation and iron deficiency is demonstrated in brain [5, 14]. Severity of RLS increases in patients with iron deficiency anemia due to decreased peripheral iron levels. This may be a result of impaired iron transport across blood brain barrier and dysfunction of transport mechanism which is responsible for importing iron into neuronal cells. Evidence from immunohisto-

chemical and protein expression techniques suggests that RLS could be a result from destabilization of transferring receptor mRNA due to defect with in iron regulatory protein 1, which ultimately cause impaired iron transport within specific brain regions like substantia nigra (neuromelanin cells)[19]. Dopamine deficiency may also play a major role in pathogenesis of RLS[19]. The dopamine receptor down-regulation coupled with low dopamine activity at night may lead to dopamine deficiency and cause RLS symptoms at night[14]. Patients who are receiving low dose of dopamine agonists showed improvement in RLS symptoms[15].

Secondary RLS

Pregnancy: Pregnancy is the most common condition associated with secondary RLS. Prevalence of RLS in pregnancy is ranged from 10-34%. The severity was reported to be highest during the third trimester[9,10]. It has shown that prevalence of RLS is more in multiparous women compared to nulliparous women[9]. The pathophysiology of RLS during pregnancy is not clear. But factors like decreased iron/ferritin levels, decreased folate levels, inadequate supplementation of iron and folate are the risk factors leading to RLS in pregnancy[10]. Iron levels tend to decrease during each pregnancy if iron stores are not restored to normal during intervals between each pregnancy [10]. Hormones like estrogens, progesterone, prolactin, and thyroid hormones play a major role in pathophysiology and development of RLS in pregnancy conditions[9, 10]. In normal physiology during pregnancy, all the hormones increases to peak level and may trigger RLS[9,10]. Physiological conditions like anxiety, stress, tension, fatigue, and insomnia may increase the symptoms of RLS during pregnancy which lead to increased incidence of day time sleepiness, PLMS and nocturnal leg cramps[9, 10]. Treatment of RLS in pregnancy should be considered a balance between the benefits of relieving symptoms and fetal risk[10].

Hypertension, CVD and cerebrovascular disease: RLS patients have reported a greater risk of stroke, coronary heart disease, myocardial infarction and cerebrovascular events. Untreated sleep disorders like insomnia, obstructive sleep apnea along with PLMS may lead to uncontrolled hypertension, CVD and stroke. Proper treatment to RLS may lead to decreased risk of CVD. Dopaminergic agents has shown reductions in sensory discomfort, improvement in sleep, decreased BP and reduced the incidence of vascular complications in patients with RLS[19]. From observational studies, it has reported that patients with RLS had slightly affected subcortical volume and more cerebral atrophy than non- RLS subjects as initiated by the MRI[19].

Diagnosis

Diagnosis of RLS is based primarily on the patient's history and neurological examination to exclude differential diagnoses[1].

The diagnosis can be made if all the following five criteria are met (International RLS Study Group [IRLSSG] diagnostic criteria):

1. A strong urge to move the legs which is usually accompanied or caused by uncontrollable, unpleasant sensation in legs.
2. Symptoms are exclusively present or worsen during times of inactivity/rest (such as lying down, sitting for long periods).
3. Partial or total relief of symptoms by movement, such as walking/ moving of legs, stretching, atleast as long as the activity continues.
4. Symptoms get generally worse or exclusively occur during evening or at night.
5. The occurrence of the first four essential criteria must not be solely accounted for as the symptoms primary to another medical or a behavioral condition.[1, 3, 7].

Diagnostic tests

Blood tests are recommended to rule out the secondary conditions that causes RLS. Tests recommended are as follows:

a. Iron studies (for serum ferritin levels)
b. Total blood count (to exclude anemia)
c. Urea and electrolyte levels

d.Thyroid function tests
e. Vitamin B12 and folic acid levels[1].
f. Needle electromyography and nerve condition
g. Polysomnography

Guidelines

The American Academy of Neurology (AAN) summarizes guidelines for treatment of RLS in adults based upon classifications of evidence and recommendations [6, 20].

Table-2 Interventions Evaluated in Primary RLS with Classification of Evidence and A-C Recommendations**[6, 20]**

Disease condition & class of evidence	Drugs	Level A-C recommendations
➢ In moderate- severe primary RLS		
Strong evidence	Pramipexole Rotigotine Cabergoline Gabapentin Pergolide	Level A
Moderate evidence	Ropinirole Pregabalin, I.V ferric carboxymaltose, ferrous sulfate with vitamin c	Level B
Weak evidence	Levodopa Cabergoline	Level C
Insufficient evidence	Preferential use of pregabalin instead of pramipexole. Gabapentin, I.V iron sucrose, oxycodone, clonazepam, clonidine, selenium, rifaximin, botulinum neurotoxin, valproic acid and Carbamazepine	Level U Level U
➢ In patients with secondary RLS associated with end-stage renal disease/ hemodialysis		
Moderate evidence	Vitamin C and E supplementations	Level B
Weak evidence	Ropinirole, levodopa or exercise	Level C
Insufficient evidence	Gabapentin or I.V iron dextran associated with ESRD/HD	Level U

Level A: Strong evidence; Level B: Moderate evidence; Level C: Weak evidence; Level U: Insufficient evidence.

Treatment

Treatment for RLS depends on severity and frequency of symptoms[1]. Pharmacological treatment includes class of drugs like dopaminergic agents, benzodiazepines, opioids, anti epileptic drugs and iron supplements. Rotigotine transdermal patch and ropinirole are highly effective in treatment of RLS[13]. Treatment for RLS starts with low doses of drugs and initiated to take 1-2 hours before going to sleep for better drug effects[5].

Dopaminergic agents

Dopamine agonists are the first-line agents used in treatment of RLS. They include carbidopa, levodopa, ropinirole, pramipexole. Levodopa given at bed time (1-2 hours before sleep) has improved quality of sleep and can improve sensory symptoms in PLMS/RLS. Levodopa at a dose of 100-200 mg once daily orally at bedtime is effective in treating RLS symptoms. Even at low doses (50-200mg) levodopa is effective in reducing RLS symptoms. Commonly seen adverse effects with levodopa are nausea, constipation, diarrhea, muscle weakness, somnolence and headache. The major drawback seen with levodopa is worsening or augmentation of RLS symptoms[5,13].

a) Ergot derivatives

Ergot derivatives which are used in treatment of RLS include pergolide, cabergoline, lisuride and bromocriptine. Pergolide at a dose of 0.4-0.5mg/day is effective in treating primary RLS. Cabergoline at a dose of 0.5-2 mg/day is effective. Bromocriptine at a dose of 7.5mg is recommended in treating RLS. In secondary RLS condition with chronic hemodialysis, short term administration of pergolide at a dose of 0.25mg/day is probably effective.

Adverse effects with ergot derivatives are nausea, headache, nasal congestion and dizziness[13]. High doses should be avoided as they cause valvular insufficiency. Patients receiving ergot derivatives for long term are recommended to obtain echo cardiogram and clinical cardiac assessment every 3-6 months interval[13].

Dopaminergic Augmentation: Augmentation refers to worsening of symptoms which commonly seen in RLS patients after a long term treatment with dopamine agonists. The greater incidence of augmentation is seen with levodopa. To prevent augmentation α2δ agonists should be initiated in RLS treatment, as they are effective and shows low risk of augmentation [6, 21].

b) Non-Ergot derivatives

Non ergot derivatives like pramipexole, ropinirole and rotigotine are used in the treatment of RLS[13].

Ropinirole: Ropinirole was subjected to be the most effective drug used in reducing symptoms of RLS. Ropinirole at a dose of 1.9mg/day has shown significant reduction of RLS symptoms and improved quality of life. It is rapidly absorbed orally and shows peak concentration in approximately 1-2 hours. It is metabolized in liver into inactive metabolites and excreted as unchanged drug in urine. Its elimination half-life is approximately 6 hours. Even at low doses of 0.25-0.5mg/day during first week of treatment is highly effective in reducing severity of RLS. However the benefits of ropinirole appeared to maintain in long term use. Ropinirole shows mild to moderate adverse effects like nausea, dizziness, headache and somnolence[3,13].

Rotigotine: Rotigotine which is a non ergot dopamine agonist has developed as a transdermal patch for the effective treatment of RLS. Rotigotine transdermal patch offers a highly effective, safe and efficacious alternative in treatment of RLS with a low risk of augmentation. This patch was withdrawn from the market in 2008 due to crystal formation in the patches. Finally the drug was authorized by FDA in 2012 for treatment of RLS. Most frequently seen adverse effects were application site reactions, erythema, pruritus, dermatitis, nausea and headache.

Benzodiazepines

Benzodiazepines particularly clonazepam is beneficial in the treatment of RLS. Benzodiazepines can improve quality of sleep and to maintain sleep in RLS patients. These drugs act as hypnotic agents, reducing sleep latency, prolonging sleep time and reducing the waking after sleep onset. Frequently known adverse effects are increased risk of falling, sedation, drowsiness, dizziness, ataxia, muscular in-coordination and behavioural changes like aggressiveness, irritability, agitation and hyperkinesis[23].

Opioids

Opioids like oxycodone and propoxyphene are used in treatment of RLS. In primary RLS, oxycodone at a mean dose of 11.4mg/day has shown improvement in RLS symptoms. Adverse effects seen with oxycodone are mild sedation, nocturnal respiratory disturbances. There is insufficient evidence about use of opioids in secondary RLS[13].

Table-3 Pharmacological Treatment of RLS with dose, time of full therapeutic effect and adverse effects[1, 7].

Medication	Dose	Time of effect of therapeutic dose	Adverse effects
Ropinirole	0.25-4.0mg	4-10 days	Augmentation, impulse disorder, nausea, low blood pressure, headache and nasal congestion
Rotigotine (transdermal patch)	1-3mg/day	1 week	Application site reactions, erythema, dermatitis, skin irritation, dizziness, headache
Pramipexole	0.125-0.75mg	At first dose	Augmentation, impulse disorder, nausea, low blood pressure, headache, somnolence and nasal congestion
Levodopa/ Carbidopa	50-200mg/ 12.5-50mg	At first dose	High rates of augmentation and loss of efficacy with rebound phenomena

Gabapentin	300-2400mg	3-6 days	Sleepiness, dizziness and fluid retention
Pregabalin	25-300mg	3-6 days	Sleepiness, dizziness, headache and fluid retention
Prolonged release oxycodone/ naloxone	5-60mg/ 2.5-30mg	1 week	Constipation, nausea, dizziness, addiction, increased sleep apnea, fatigue, pruritus and dry mouth
Clonazepam	0.5mg-2.0mg	At first dose	High risk of sleepiness, dizziness, morning drug hangover
Tramadol	50-100mg	At first dose	Dizziness, nausea, sweating, constipation, fatigue, dry mouth and augmentation
Methadone	5-40mg	At first dose	Fatigue, constipation, sedation, flush depression and anxiety
Ferrous sulphate	200mg three Times daily	2-3 weeks	Constipation

Anti Epileptics

Anti-epileptics agents like Carbamazepine, gabapentin, lamotrigene, valproate and topiramate are used in the treatment of RLS. In primary RLS, Carbamazepine at a dose of 100-300mg daily at bedtime has shown improvement in the frequency of RLS symptoms and reduced the RLS attacks in long term use. Adverse effects with carbamazepine are less serious. Gabapentin at a dose of 800-1800 mg/day is effective in the treatment of primary RLS. Gabapentin lead to discontinuation due to adverse effects like somnolence and lethargy[13].

Iron Treatment

RLS severity is associated with low ferritin levels. Oral iron treatment is recommended as first line therapy. IV iron should be recommended in conditions whenever serum ferritin levels are too high for oral iron absorption, when oral iron is not tolerated or contraindicated or when there is inadequate response to oral iron. Oral iron treatment for adults with RLS includes ferrous sulphate 325mg (65mg elemental iron) twice a day with 100mg vitamin C twice daily for patients with serum ferritin levels ≤75µg/L. Ferric carboxymaltose 1000mg is considered effective for the treatment of moderate to severe RLS in patients with serum ferritin level < 300µg/L. Side effects include nausea and headache. RLS with iron deficiency anemia has shown to respond well to 1000mg of IV LMW iron dextran[24].

Patient Education

Non-pharmacological treatment includes avoiding caffeine, alcohol and nicotine which may help to improve RLS symptoms. Walking, moving/ stretching of legs and regular motor activities help in reducing symptoms[1]. Temporary relief is seen with hot and cold baths, rubbing or massaging the legs before sleep[5]. Patients with RLS should avoid severe stress conditions and should maintain proper sleep hygiene[7]. Other non-pharmacological management includes cognitive therapy, vibration pads, yoga, compression devices and acupuncture which improve sleep disorders including RLS[20]. Sleep hygiene (sleep in a quiet, comfortable, peaceful environment and keep regular bed and wake hours) should be established[1]. Secondary causes of RLS and exacerbating factors should be recognized and treated as soon as possible. They include managing renal impairment, treating low serum ferritin levels and eliminating anti-dopaminergic agents[25].

Conclusion

RLS is a familial disorder. Prevalence of RLS is 2-15 % among general population and it appears more in Northern and Western European countries. Dopaminergic agents are preferred to be first line treatment for RLS. Among them, non ergot derivatives like Ropinirole and Rotigotine transdermal patch are mostly used. Preventive measures include avoiding stress conditions, maintaining proper sleep hygiene and cognitive therapy.

Abbreviations

RLS – Restless Legs Syndrome
GWAS – Genome Wide Association Studies
MRI – Magnetic Resonance Imaging
PLMS – Periodic Limb Movements of Sleep
CVD – Cardiovascular Disorder
PSG –Polysomnography
FDA – Food and Drug Administration

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