REVIEW ARTICLE

# Restless legs syndrome: Common yet an under recognized entity

**Dipti Gothi**

Associate Professor Pulmonary Medicine, Department of Pulmonary Medicine, Employees State Insurance Post Graduate Institute of Medical Sciences & Research (ESI-PGIMSR), New Delhi, India.

***DOI No:*10.5958/0974-0155.2014.01103.6** *Indian J Sleep Med 2014; 9.2, 41-49*

## Abstract

Restless legs syndrome (RLS) or Willis–Ekbom disease is a common yet an underrecognized disease despite the fact that awareness is the only equipment required to diagnose this condition. The RLS is diagnosed with four essential criteria that can be abbreviated as "URGE," that is,urge to move, rest induced, gets better with activity, and evening and night accentuation. Periodic limb movementsduring sleep (PLMS), a component of RLS, in 90% cases needs to be differentiated from RLS as PLMS may also be seen with disorders such as obstructive sleep apnea, upper airway resistance syndrome, narcolepsy, and rapid eye movement sleep disorder in 70% cases. Diagnosis of PLMS contrary to RLS requires sleep study. This review was aimed at increasing awareness about RLS; differentiating RLS from PLMS; and pathogenesis, management options, and recent advances for RLS.

**Keywords:** Restless legs syndrome, periodic limb movements during sleep.

## Introduction

Restless legs syndrome (RLS), described first in 1945 and also known as Willis–Ekbom disease (WED), is a disorder that leads to abnormal sensations in the extremity,especially legs[1]. Though it affects legs and predominantly presents to general physician or neurologist, it can present to almost all specialties. It is often associated with periodic limbmovements during sleep (PLMS). Insomnia, sleep disturbance, or excessive daytime sleepiness (EDS) can be its presenting manifestation. Thus, it is extremely important for a practicing sleep physician to be aware about this disease that can be easily diagnosed and treated. Yoakum[2] has described RLS as "the most common disorder you've never heard of," which is an appropriate description of RLS. Definite diagnostic criteria have been laid down and evidence-based guidelines are available for the management. But it is crucial for the practicing physician to cross the very first hurdle of asking about symptoms of RLS in all the patients who present with sleep disturbance or EDS. Increasing awareness about the disease in the practicing physician,especially sleep physician, is an important step toward appropriate management of this common yet highly underdiagnosed disease. Box 1 gives summary of this review.

*Address for correspondence*

**Dr. Dipti Gothi**
Associate Professor Pulmonary Medicine
Department of Pulmonary Medicine,
Employees State Insurance Post Graduate
Institute of Medical Sciences & Research
(ESI-PGIMSR), New Delhi, India
Email: diptigothi@gmail.com

**Box 1: Summary**

- Restless legs syndrome (RLS) is described as "the most common disorder you've never heard of" by Yoakum[2]
- There are no population-based studies from India; however, studies from other countries estimate a prevalence ranging from 9% to 15% on the basis of a single question.
- The pathogenesis is possibly an interplay of hypoxia, iron transport, and dopaminergic system.
- The essential diagnostic criteria consist of "URGE," that is, urge to move, rest induced, gets better with activity, and evening and night accentuation.
- RLS can be idiopathic or secondary to anemia, uremia, diabetes, parkinsonism, etc.
- RLS needs to be differentiated from periodic limb movements during sleep (PLMS) because 80%–90% patients with RLS have PLMS but only 30% patients with PLMS have RLS.
- PLMS can be associated with obstructive sleep apnea, upper airway resistance syndrome, rapid eye moment sleep disorder, and narcolepsy.
- PLMS is diagnosed by polysomnography whereas RLS diagnosis is only based on history.
- Only 20% RLS require pharmacological treatment.
- The first-line pharmacological agents are dopamine-receptor agonist (e.g., pramipexole) or a2 calcium-channel ligand (e.g., pregabalin); both these can loose efficacy over time.
- Augmentation of symptoms and impulse control disorder are problems with dopamine-receptor agonist, and depression and excessive daytime sleepiness are problems with 2 calcium-channel ligand.

## Epidemiology of RLS

From India, no studies are available on the prevalence of RLS in general population. From among the studies that have tried to gauge the gravity of problem, one study had concluded that 2.9% patients with sleep-related disorders have RLS[3]. However, it was not a direct questionnaire-based study to know the exact prevalence of RLS in general population. In yet another Indian study, of 653 subjects with insomnia or leg pain, 15.31% subjects had RLS[4]. Studies from other countries in general population have estimated a prevalence ranging from 9% to 15% on the basis of a single question, whereas studies that tried to rule out an alternative diagnosis have estimated the prevalence of 1.9%–4.6%[5,6]. In India, anemia and diabetes, which are predisposing factors for RLS, are widely prevalent. Hence, Indian population is likely to have higher prevalence. The age of onset varies widely, from childhood to over 80 years of age[7]. The prevalence is about two times higher in women than in men and increases with age[5].

## Clinical Presentation of RLS

RLS is a somatosensory network disorder with an urge to move and usually, but not exclusively, affects the legs. The sensory symptoms may include pricking, crawling, aching, burning, pulling, itching, and tingly sensations. Sometimes they could be as unique as "colas in my veins." Patients experience these symptoms usually in the evening while sitting. The symptoms may prevent patients from going to bed. Patients may complain of having to get up from the bed either to stretch their legs or walk a few paces before they can return to the bed, only to be troubled by the same symptoms again[8].

## Pathogenesis of RLS

The exact pathogenesis of RLS is not known. Clinical observations suggest the role of dopaminergic pathway as dopaminergic drugs alleviate the symptoms and dopamine antagonists trigger or exacerbate them[5]. The impairment in dopaminergic system is functional and metabolic rather than anatomical. Studies imply that the functional and metabolic alteration is characterized by upregulation of dopaminergic transmission, with

postsynaptic desensitization[5].The dopaminergic transmission alteration is possibly at the level of central nervous[9] structures and networks via nigrostriatal and mesolimbic pathways[10]. Functional magnetic resonance imaging (MRI) and positron emission tomography studies have pointed the area of involvement as medial thalamus, which is a part of limbic system[11]. There are studies using a resting-state functional MRI, which suggest that there is a deficit in controlling and managing sensory information leading to disruption of sensorimotor processing[12]. Furthermore, MRI studies using iron-sensitive sequences have shown reduced iron content in several regions of brain[10]. Though most studies have implicated the role of central nervous system, one of the recent studies has suggested the possibility of significant peripheral hypoxia in the legs of patients with RLS during the symptomatic period. This study was based on transcutaneous measurement of $pO_2$[13]. Overall, possibly there appears to be activation of hypoxia-inducible factor pathway due to iron deficiency, which in turn leads to increase in tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis) altering dopaminergic system with a genetic overtone in the implication of RLS[14].Afamily history of RLS is common and twin studies have shown heritability estimates of 54%–83%[5].

## Diagnostic Criteria of RLS

There are four essential diagnostic criteria first defined in 1995 and subsequently revised in 2003[15,16]. The diagnosis does not require any laboratory test, but it is essential to fulfill all the criteria:

- An urge to move the legs, usually associated with unpleasantlegsensations
- Exacerbation of symptoms by rest
- Symptom relief on activity
- Symptoms worse in the evening and at night

The pneumonic for the same can be "URGE"[17]: urge to move, rest induced, gets better with activity, and evening and night accentuation. Apart from these, the following supportive/additional features can be present[1]:

- Dopaminergic drug responsiveness
- Periodic limb movements with arousal, PLMS
- Positive family history
- Chronic progressive course with periodic exacerbations
- Normal neurological examination (except neuropathy)
- Sleep disturbance

## Classification of RLS

There are two types of RLS[8]:

1. *Early onset RLS*: The age of onset is less than 45 years, tends to cluster in families, and progresses slowly with a female-to-male ratio of 2:1.
2. *Late-onset RLS*: The age of onset is more than 45 years; has an equal male-to-female ratio;has more rapid progression;has more severe and more frequent symptoms;has no familial clustering; and are more commonly associated with radiculopathy, neuropathy, or myelopathy.

On the basis of etiology, RLS can be divided into idiopathic or secondary. Secondary is commonly due to iron deficiency anemia and uremia. The other diseases, which may be associated with RLS, are cardiovascular disease, obesity, diabetes, chronic obstructive pulmonary disease, rheumatological disorders, peripheral neuropathy, radiculopathy, Parkinson's disease, multiple sclerosis, Charcot–Marie–Tooth disease, and spinal cord lesions[5].

## Diagnostic Workup

It is essential to do complete blood count, iron studies (s ng sleep (PLMS),which are described as parasomnias. PLM most commonly involve the lower limbs and in severe cases may resemble the Babinski reflex[21].Contrary to RLS, the PLMS is diagnosed only on polysomnography. Both RLS and PLMS share the same pathophysiology and management is also the same when they co-occur. However, only 30% patients with PLMS have RLS, 80%–90% patients with RLS have PLMS[8].If PLM occur in awake state,they are called periodic limb movements of wakefulness.

## Difference between PLMS and RLM

Periodic limb movements (PLM) are types of motor disorder that occur typically in sleep called periodic limb movements during sleep (PLMS),which are described as parasomnias. PLM most commonly involve the lower limbs and in severe cases may resemble the Babinski reflex[21].Contrary to RLS, the PLMS is diagnosed only on polysomnography. Both RLS and PLMS share the

same pathophysiology and management is also the same when they co-occur. However, only 30% patients with PLMS have RLS, 80%–90% patients with RLS have PLMS[8].If PLM occur in awake state,they are called periodic limb movements of wakefulness.

## Diagnosis of PLMS

The diagnosis of PLMS requires polysomnography. During the study, it is essential to place anterior tibialis electrodes to record the leg movements. Surface electrodes should be placed longitudinally and symmetrically around the middle of the muscle so that they are 2–3 cm apart orone-third of the length of the anterior tibialis muscle, whichever is shorter. PLMS scoring rule as per American Academy of Sleep Medicine is as follows[22]:

- The minimum duration of leg movement event: 0.5–10 s.
- The amplitude: 8 ìV above the baseline.
- PLMS series is defined as more than four leg movements separated by at least 5 s but not more than 90 s.
- They can be either associated with EEG arousals or in severe cases even with overt arousals.

The PLM Index (PLMI) is calculated by dividing the total number of PLMS by sleep time in hours. PLMI of >5 and <25 is considered mild, PLMI of >25 and <50 is considered moderate, and PLMI of >50 is considered severe[8].

## Types of PLMS

There are two types of PLMS: Type I and II. Type I (spontaneous) has peak frequency between midnight and 3 a.m. followed by decrease in late morning hours. Type II has more even distribution throughout the night. This type is associated with sleep-related breathing disorders such as obstructive sleep apnea (OSA), upper airway resistance syndrome (UARS), rapid eye movement (REM) sleep disorder, and narcolepsy[8]. The PLMS due to RLS versus other sleep disorders can be easily differentiated by simple history taking. Thus, all the sleep proformas must contain detail questioning on RLS otherwise it can be missed. Box 2 enumerates an example of RLS associated with PLMS, which was missed on initial evaluation.

**Box 2: An example of RLS with PLMS**

A 65-year-old woman was referred to sleep clinic for suspected obstructive sleep apnea (OSA). OSA was suspected because the woman was obese with body mass index of 31.5 kg/m$^2$, snoring, disturbed sleep, diabetes, and excessive daytime sleepiness (EDS) with Epworth sleepiness score of 21. The resident doctor administered detailed sleep questionnaire and gave appointment for overnight polysomnography. On reviewing the sleep study, only poor sleep efficiency was detected. The patient was called to give the report. Detailed interview confirmed disturbed sleep and severe EDS. The patient was then questioned about symptoms of restless legs syndrome (RLS). The study was reviewed, and the technician was interviewed about placement of electrodes. The technician had forgotten to place the anterior tibialis electrodes, hence PLMS were not picked up. All the criteria for RLS were satisfied and the repeat study was performed. An epoch of the study is given in Figure 1. Her periodic limb movements (PLM) Index was 148 per hour with PLM arousal index of 10.2 per hour. She was treated with a2 ligand.

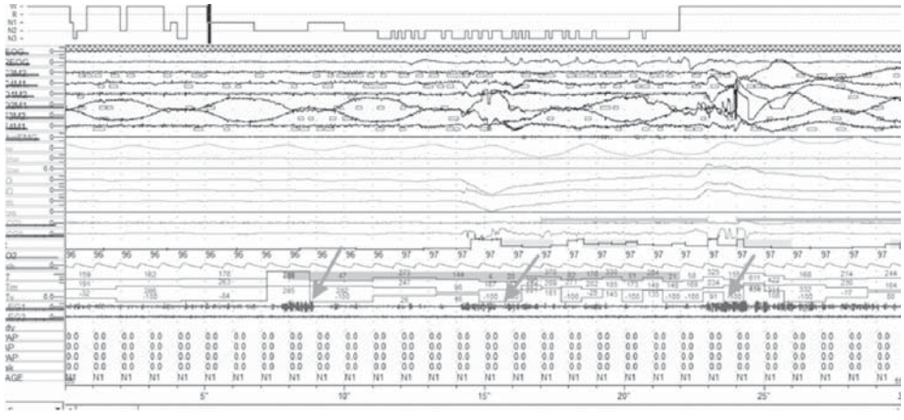

**Figure 1: An epoch of patient with RLS with PLMS showing PLMS series (marked with arrows)**

## Management of PLMS

Treatment of PLMS due to RLS (type I) is same as treatment of RLS (given in management of RLS section). The treatment of type II PLMS requires treatment of the primary cause,that is, OSA, UARS, or narcolepsy.

## Differential Diagnosis of RLS

RLSneeds to be differentiated from akathisia (a feeling of motor restlessness associated with dopamine receptor blocking neuroleptic agents), nocturnal cramp, positional discomfort, peripheral neuropathy,parkinsonism with sensory symptoms, arthritis, hypnic jerks, fibromyalgia, and varicose veins. A careful history and examination differentiates RLS from others[1,5,23]. A definite diagnosis can be made if all the criteria are satisfied as no other diseases can cause "URGE" symptoms[1,5]. If all the criteria are not satisfied, a neurology opinion must be taken.

## Consequences of RLS

RLS has a large impact on quality of life, similar to that of type 2 diabetes and osteoarthritis[24,25].Women with RLS have an elevated risk of coronary heart disease[26]. Emerging evidence also suggests that RLS is associated with metabolic dysregulation and autonomic dysfunction. It has been shown that RLS is probably associated with diabetes and impaired glucose tolerance[27]. Increased symptom severity is also associated with serious psychological impairment and insomnia[6,28].

## Course of RLS

The clinical course of RLS varies considerably. The appearance of symptom in younger patients (<30 years) is usually insidious and in elderly (>50 years) it is abrupt[29].On the basis of the progression of disease, it may be divided into (a) Intermittent RLS where symptoms are intermittent, justify treatment intermittently, and may remit spontaneously; (b) daily RLS,which have daily symptoms and require daily therapy; and (c) refractory RLS, which does not have satisfactory response, or response wanes with time, or intolerable side effect occurs, or uncontrollable symptom augmentation occurs[30,31].

## Management of RLS

For patients with mild or infrequent symptoms, nondrug-based options may be sufficient to provide symptom relief[5]. It has been observed that only about 20% RLS require drugs[1]. The management can be divided into following:

1. Treatment of secondary causes
2. Nonpharmacological management
3. Pharmacological management

### *Treatment of secondary causes*

Iron supplements should be given if serum ferritin is less than 112 pmol/L (50 ìg/L) irrespective of hemoglobin level, as anemia is not sufficiently sensitive marker for iron deficiency[5]. Supplemental oral/intravenous iron is also indicated for management of pregnancy-related RLS. In severe intractable cases of pregnancy-related RLS, low-dose clonazepam/carbidopa/levodopa may be given in second or third trimester[32].Drug history should be taken in all the cases, and it is essential to stop antipsychotics, antidepressants, antihistamines, dopamine receptor blocking agents such as metoclopramide and prochlorperazine, and diphenhydramine[5].

### *Nonpharmacologicalmanagement*

- Avoidance of alcohol, caffeine, and smoking.
- Avoidance of overexertion, stress, and sleep deprivation.
- Good sleep hygiene such as quiet comfortable sleep environment, avoiding TV during bedtime, appropriate nightwear, and regular sleep pattern.
- Going to bed late may help as RLS affects first part of cycle.
- Moderate regular exercise.
- Brief walking or other motor activities.
- Hot baths or leg massage before bedtime.
- Relaxation exercisessuch as yoga.
- Distraction by reading book,and so on.
- Pneumatic compression devices may be used in some cases. These prevent deep vein thrombosis, can alleviate RLS symptoms, and in some cases even completely resolve it[5,12,33–36].

## Pharmacological management

Pharmacological treatment is required in patients with[2,5]symptoms that seriously impair quality of life, sleep, or daytime functioning and in whom there are more than two attacks per week despite reversal of iron deficiency and removal of possible exacerbators/ secondary cause. It has been estimated that only about 20% require drugs[5]. The classes of drug useful for the management of RLS are the following[35]:

- Dopaminergic agents, which can be divided into non-ergot-derived dopamine-receptor agonists (e.g.,pramipexole), dopamine precursor (e.g., levodopa), and ergot-derived dopamine-receptor agonists (e.g.,pergolide and cabergoline)
- α2 Calcium-channel ligands (e.g., gabapentin andpregabalin)
- Opioid agonist (e.g., tramadol and methadone)
- Benzodiazepines (e.g., clonazepam)
- Anticonvulsant (e.g.,valproicacid)

The details about commonly used drugs are given in Table 1.Non-ergot-deriveddopaminergic agents,that is,ropinirole, pramipexole (immediate/extended release), and rotigotine (patch), are the most extensively investigated and effective therapies for the treatment of RLS and generally considered the first-line agents. However, there are two major problems with dopaminergic drugs: augmentation and impulse control disorder (ICD). Augmentation leads to increased severity of symptoms; or the spread of symptoms to different body parts, such as the arms, trunk, or even face. Augmentation is common with long-acting agents, higher dosage, and low transferrin levels (<75ìg/mL)[5,37,38]. ICDs are pathological gambling, compulsive shopping, hypersexuality, and compulsive eating[39]. ICDs are associated with higher dose, history of experimental drug use, female sex, and a family history of gambling disorders[5]. In case of augmentation or ICD, it is recommended that 2 calcium-channel ligands should be given instead of non-ergot-deriveddopaminergic agents. Apart from augmentation, non-ergot-deriveddopaminergic agents can have rebound phenomenon, which is characterized by appearance of symptoms in the morning as the effects of a medication wear off[40]. These can be managed by giving long-acting non-ergot-deriveddopaminergic or changing into another class of drug.

**Table 1: Pharmacological management of RLS[26]**

| Drug | Class of drug | Dosage | Side effects | Indication |
|---|---|---|---|---|
| Pramipexole | Non-ergot-derived dopamine-receptor agonists | 0.125–0.75 mg daily | Sleepiness (5%–56%), nausea (12%–25%), insomnia (7%–16%), ICD, LOE, augmentation, rebound phenomenon | Severe symptoms, excessive weight, metabolic syndrome, OSA, comorbid depression |
| Rotigotine | Non-ergot-derived dopamine-receptor agonists | 1–3 mg transderm al patch | Application-site reactions to the patch (22%–58%), nausea (7%–19%), headache (4.1%–10.8%), fatigue (0.5%–11%), lower rates of augmentation than pramipexole/r opinirole, ICD, and LOE | Severe daytime symptoms in addition to indications of pramipexole |
| Ropinirole | Non-ergot-derived dopamine-receptor agonists | 1.6–2.0 mg | Nausea (25%–50%), headache (7%–22%), fatigue (1%–19%), dizziness (6%–18%), vomiting (5%–11%), ICD, LOE, augmentation, rebound phenomenon | Same as pramipexole |
| Levodopa-carbidopa | Dopamine precursor | 200- and 700-mg daily | LOE and augmentation are much more common compared to pramipexole/r otigotine/ropi nirole/pregaba lin and gabapentin, nausea | If other drugs such as pramipexole/preg abalin are not available |
| Pregabalin | α2 Calcium-channel ligands | 100–300 mg/day | Somnolence (19.7%–41%), dizziness (11.5%–46%), and headache (7.2%–12.6%), weight gain, depression, | Painful RLS, comorbid pain, history of ICD, substance abuse, comorbid insomnia, anxiety, severe sleep disturbance |
| Gabapentin enacarbil | α2 Calcium-channel ligands | 300 mg/day | Dizziness (21%), somnolence (18%), fatigue (11%), and nausea (10%), weight gain, depression, LOE (least common) | Same as pregabalin |
| Methadone | Opioid receptor agonist | 5–40 mg/day | Sedation, depression or anxiety, altered consciousness | RLS refractory to other treatments and loss of efficacy to other agents, augmentation |

ICD, impulse control disorder; LOE, loss of efficacy; OSA, obstructive sleep apnea.

Dopamine precursors (e.g., levodopa-carbidopa) though are effective, loose efficacy very soon and lead to frequent side effects, hence are not commonly used in the management[35]. Ergot-derived dopamine-receptor agonists (e.g.,pergolide and cabergoline) lead to valvulopathy, hence cannot be used in the treatment[35].

α2 Calcium-channel ligands (i.e., gabapentin enacarbil, and pregabalin) are generally well tolerated with self-limiting side effects and all the drugs in this group have similar efficacy and side effect profile[35]. Recent findings comparing pramipexole with pregabalin suggest that pregabalin is more effective and has significantly lower rates of augmentation compared to pramipexole. However, suicidal tendencies are higher with pregabalin[41].

Both non-ergot-deriveddopaminergic and a2 calcium-channel ligands tend to loose efficacy over time. In these cases with loss of efficacy, consideration should be given to adding another medication or changing medications instead of increasing the dosage of the drug, which is being used[35].

Methadone (i.e., opioid agonist) is indicated only in refractory cases or patients with severe augmentation and both dopaminergic agents and a2 calcium-channel ligands have not been useful in alleviating the symptoms. There have been very few studies on clonazepam and valproic acid, and these studies have not proved the efficacy of these drugs. Hence, they are not recommended for the management unless all above have failed or cannot be given[42,43].

## Variants of RLS

- *Burning mouth syndrome*: It is an oral dysesthesia leading to burning sensation of the tongue, oral mucosa, and perioral mucosa. Some of these patients fulfill the criteria for RLS and respond to levodopa[44].
- *Restless genital syndrome*: Symptoms in the genital region, such as pain, discomfort, tingling, and burning sensations, with either restless legs or symptoms of an overactive bladder, in the absence of conscious feelings of sexual desire.Lidocaine, oxazepam, clonazepam, tramadol, and transcutaneous electrical nerve stimulation, combined with psychotherapeutic counseling, have been described as the most appropriate treatment modalities for restless genital syndrome[45,46].

To conclude RLS is a common yet underrecognized entity with the prevalence of 9%–15% from other countries. Population-based studies from India are needed to know the exact prevalence in India.The pathogenesis possibly involves hypoxia–iron transport–dopaminergic interplay.It can be easily diagnosed by diagnostic criteria of "URGE." Sleep physician need to understand the difference between RLS and PLMS, both of which are not mutually exclusive. PLMS can be associated with other sleep disorders such as OSA, UARS, narcolepsy, and REM sleep disorder. Treatment of RLS and PLMS secondary to RLS consists of dopamine-receptor agonist or a2 calcium-channel ligand as the first-line treatment for most patients, with the choice of agent dependent on the patient's severity of RLS/WED symptoms, cognitive status, history, and comorbid conditions. Augmentation of symptoms and ICD needs to be kept in mind while treating with dopamine-receptor agonist whereas depression and EDS needs to be taken care of while treating witha2 calcium-channel ligand. Loss of efficacy is the common problem in treatment of RLS; adding another medication or changing medications is recommended for the same.

## References


1. **Byrne R,** Sinha S, Chaudhuri KR. Restless legs syndrome: diagnosis and review of management options. *Neuropsychiatr Dis Treat* 2006; 2(2): 155–64.
2. **Yoakum R**. Night Walkers: Do Your Legs Seem to have a Life of Their Own? Your Torment has a Name. *Modern Maturity*September-October 1994;55:82–4.
3. **Panda S,**Taly AB, Sinha S, Gururaj G, Girish N, Nagaraja D. Sleep-related disorders among a healthy population in South India. Neurol India 2012; 60:68–74.
4. **Gupta R,**Lahan V, Goel D. Restless Legs Syndrome: a common disorder, but rarely diagnosed and barely treated—an Indian experience. *Sleep Med* 2012;13: 838–41.
5. **Leschziner G,**Gringras P. Restless legssyndrome. *BMJ* 2012;344:e3056.
6. **Ohayon MM,** O'Hara R, Vitiello MV.Epidemiology ofrestless legs syndrome: a synthesis of the literature. *Sleep Med Rev*2012;16(4):283–95.
7. **Winkelmann J,** Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. *Sleep* 2000;23:597–602.
8. **Natarajan R**. Review of periodic limb movement and restless leg syndrome. *J Postgrad Med* 2010;56:157–62.

9. **Wetter TC,**Eisensehr I,Trenkwalder C. Functional neuroimaging studies in restless legs syndrome. *Sleep Med*2004;5:401–6.
10. **Rizzo G,**Tonon C, Manners D, Testa C, Lodi R. Imaging brain functional and metabolic changes in restless legssyndrome. *CurrNeurolNeurolNeurosci Rep* 2013;13:372.
11. **Rizzo G,**Tonon C,Testa C,Manners D,Vetrugno R,Pizza F,et al. Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. *Brain* 2012;135:3712–20.
12. **Ku J,** Cho YW, Lee YS, Moon H, Chang H, Christopher J, et al. Functional connectivity alternation of the thalamus in restless legs syndrome patients during the asymptomatic period: a resting-state connectivity study using functional magnetic resonance imaging. *Sleep Med* 2014; 15: 289–94.
13. **Salminen A,** Polo O. Peripheral hypoxia in patients with restless legs syndrome.*Sleep Med* 2013;14:e39–40
14. **Earley CJ,** Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis–Ekbomdisease). *Sleep Med* 2014;15: 1288–301.
15. **Walters AS.** Toward a better definition of restless legs syndrome. The International Restless Legs Syndrome Study Group. *MovDisord* 1995;10:634–42.
16. **Allen RP,**Picchietti D, Hening WA,Trenkwalder C, Walters AS, Montplaisi J, et al. 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;4:101–19.
17. **Hening W,**Allen RP,Tenzer P,Winkelman JW. Restless legs syndrome: demographics, presentation, and differential diagnosis.*Geriatrics*2007;62:26–9.
18. **Klingelhoefer L,**Cova I, Gupta S,Chaudhuri KR. A review of current treatment strategies for restless legs syndrome (Willis–Ekbom disease). *Clin Med* 2014;14: 520–4.
19. **Walters AS,**LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome.*Sleep Med* 2003;4: 121–32.
20. **Gupta R,**Lahan V,Goel D. Translation and validation of International Restless Leg Syndrome Study Group rating scale in Hindi language. *Ann Indian AcadNeurol* 2011;14:257–61.
21. **Rijsman RM,** de Weerd AW. Secondary periodic limb movement disorder and restless legs syndrome. *Sleep Med Rev* 1999;3:147–58.
22. **Iber C,**Ancoli-Israel S, JrChesson AL,Quan SF. The AASM Manual for the Scoring of Sleep and Associate Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine,Westchester, IL, 2007.
23. **Garcia-Borreguero D,**Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodríguez VM, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. *BMC Neurol* 2011;11:28.
24. **Allen RP,** Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286–92.
25. **Happe S,** Reese JP, Stiasny-Kolster K, Peglau I, Mayer G, Klotsche J, et al. Assessing health-related quality of life in patients with restless legs syndrome. *Sleep Med* 2009;10:295–305.
26. **Li Y,** Walters AS, Chiuve SE, Rimm EB, Winkelman JW,Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation* 2012;126:1689–94.
27. **Innes KE,**Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. *Sleep Med Rev* 2012;16(4):309–39.
28. **Winkelman JW,** Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. *Sleep* 2009;32:772–8.
29. **Allen RP,**Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. *Sleep Med* 2000;1:11–19.
30. **Ondo W,**Jankovic J. Restless legs syndrome: clinicoetiologic correlates. *Neurology* 1996;47(6):1435–41.
31. **Allen RP**. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med* 2007;120(1 Suppl 1):S13–21.
32. **Lutz EG**. Restless legs, anxiety and caffeinism. *J Clin Psychiatry* 1978;39:693–8.
33. **Aldrich MS,** Shipley JE. Alcohol use and periodic limb movements of sleep. *Alcohol ClinExp Res* 1993;17:192–6.
34. **Russell M**. Massage therapy and restless legs syndrome. *J Bodywork MovTher* 2007;11:146–50.
35. **Garcia-Borreguero D,**Kohnen R, Silber MH, Winkelman JW, Earley CJ, Hogl B, et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med* 2013;14: 675–84.
36. **Lettieri CJ,**Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. *Chest*2009;135(1):74–80.
37. **García-Borreguero D,** Williams AM. Dopaminergic augmentation of restless legs syndrome. *Sleep Med Rev* 2010;14:339–46.
38. **Trenkwalder C,**Högl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. *Sleep Med* 2008;9:572–4.
39. **Cornelius JR,**Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case control study. *Sleep* 2010;33:81–7.

40. **Kurlan R,** Richard IH, Deeley C. Medication tolerance and augmentation in restless legs syndrome: the need for drug class rotation. *J Gen Intern Med* 2006; 21:C1–4.

41. **Allen RP,** Chen C, Garcia-Borreguero D, Polo O, DuBrava S, Miceli J, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. *N Engl J Med* 2014;370:621–31.

42. **Aurora RN,**Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al.The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep* 2012;35(8):1039–62.

43. **Trenkwalder C,**Hening WA, MontagnaP, Oertel WH, Allen P, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *MovDisord* 2008;23: 2267–302.

44. **Prakash S,**Ahuja S, RathodC. Dopa responsive burning mouth syndrome: restless mouth syndrome or oral variant of restless legs syndrome?*J NeurolSci* 2012;320:156–60.

45. **Aquino CC,**Mestre T, Lang AE.Restless genital syndrome in Parkinson disease. *JAMA Neurol*2014;71(12):1559–61.

46. **Spoelstra SK,**Waldinger M,Nijhuis ER,Weijmar Schultz WC. [A woman with restless genital syndrome: a difficult-to-treat condition.][Article in Dutch] *Ned Tijdschr Geneeskd* 2013;157(16):A5805.