Restless Legs Syndrome & Periodic Limb Movement Disorder

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Restless Legs Syndrome (RLS) is a common, distressing and treatable disorder that is often misdiagnosed. The International RLS Study Group Essential Criteria for the diagnosis of RLS are: A distressing urge to move the limbs (with or without discomfort), which begins or is worse at rest or inactivity, is at least partially relieved with activity, and is worse in the evening or at night (2,3). Supportive clinical features are: A positive family history, periodic limb movements in sleep and response to dopaminergic treatment. The estimated prevalence of RLS in the United States is 10% (5).

RLS can be primary or associated with a variety of conditions, including iron deficiency (7), renal failure, pregnancy (8) and peripheral nerve disease (9,10,11). The majority of patients with RLS also have periodic limb movements in sleep (PLMS). These are periodic, involuntary limb movements comprising extension of the big toe, and triple flexion at the ankle, knee and sometimes the hip. PLMS are not specific for RLS. They can occur in normal individuals without sleep related problems, and are also seen in a variety of other sleep disorders, including obstructive sleep apnea syndrome, narcolepsy and REM sleep behavior disorder.

Periodic Limb Movement Disorder (PLMD) is often confused with RLS. PLMD is diagnosed when there is a sleep complaint such as insomnia or daytime sleepiness and polysomnography shows frequent periodic limb movements, which may be associated with arousals. The finding of PLMS alone is not sufficient to make a diagnosis of PLMD. Symptoms must be present which cannot be attributed to any other medical, psychiatric or sleep disorder. Therefore, a patient with RLS who has PLMS does not have PLMD. Regardless, the therapeutic approach to RLS and PLMD is similar (12).

Patients with RLS tend to under-report symptoms, and physicians often fail to recognize the symptom complex, and attribute the leg discomfort to other causes like nocturnal leg cramps, arthritis or nonspecific musculoskeletal pain. The diagnosis of RLS is usually evident once one's attention is drawn to it, and the 4 essential diagnostic criteria are met. The provocation by rest or inactivity, circadian rhythmicity (worse in the evenings) and rapid (though partial) relief by activity are not typical of most of the other conditions which have been mistaken for RLS.

The pathophysiology of RLS and PLMD is unknown. Genetic factors have been implicated: A positive family history is present in 40-60% of RLS patients and there is high concordance in identical twins. The prevailing hypothesis is that there is subcortical dysfunction causing decreased inhibition of lumbosacral generators of periodic limb movements. This disinhibition leads to periodic limb movements in wakefulness and in sleep characteristic of RLS associated with PLMS. The association of RLS with both large and small fiber neuropathy suggests that peripheral nerve dysfunction may also be important in the pathogenesis of RLS (10,11). The dopamine and opiate systems have

been implicated because of the excellent response of RLS symptoms to dopaminergic agents and opioids, and exacerbation of symptoms by centrally acting dopamine antagonists or naloxone. Iron deficiency is associated with RLS and iron replacement improves RLS symptoms, suggesting that abnormal iron metabolism may play a role (7).

The diagnosis of RLS is clinical, based on the 4 Essential Criteria. Initial evaluation should focus on the exclusion of associated conditions, including peripheral nerve disease. Blood testing should include ferritin levels, especially if the patient is at risk of iron deficiency anemia, such as having a history of bleeding or regular blood donation. In primary RLS without other suspected conditions, usually no other specific testing is needed. EMG and small fiber studies may be indicated if peripheral nerve disease is suspected. Polysomnography is not routinely indicated unless another sleep disorder such as obstructive sleep apnea is suspected. The presence of PLMS supports, but is not needed, for the diagnosis of RLS.

The management of RLS is divided into behavioural and pharmacological interventions. In general counterstimulation (rubbing legs, hot baths), good sleep hygiene, regular exercise, reduced caffeine and alcohol intake, and avoidance if possible of drugs which exacerbate RLS (most antidepressants, neuroleptic agents and antihistamines) are recommended. Patients with mild, infrequent RLS may benefit from these behavioral techniques alone, and RLS drugs as needed infrequently. Patients with iron deficiency should be investigated for the underlying cause and oral iron replacement initiated. Ferritin levels should be rechecked periodically.

The main categories of drugs used for the symptomatic treatment of RLS are the dopaminergic agents, anticonvulsants (mainly gabapentin), the sedative hypnotics and opioid drugs. Drug therapy should ideally address the distressing limb sensations, as well as associated problems such as insomnia and depression. Most patients with RLS will respond to dopaminergic agents. However because of the significant problem of augmentation (about 80% with L-dopa and 30% with dopamine agonists), L-dopa is no longer considered 1st line, its use is confined to intermittent dosing to provide rapid relief for infrequent symptoms (13). For patients with severe and frequent symptoms, a dopamine agonist is generally the initial drug of choice (14-28). Gabapentin is an acceptable alternative for patients with painful RLS, those with a neuropathic component to the leg discomfort, or those who may not tolerate the side effects of dopamine agonists (29,30). Sedative-hypnotics and opioids are less often used because of the potential for dependence, tolerance, withdrawal and respiratory depression. Generally opioids are reserved for severe cases which are refractory to other drugs, or when pain is severe, or in the perioperative setting when oral medications are held.

In patients who do not respond to conventional therapy, it is especially important to rule out underlying secondary causes, including iron deficiency. If possible drugs which worsen RLS may need to be changed. In general, besides iron and folate supplements, no drugs are safe for use in pregnant patients with RLS. Secondary RLS improves when the underlying condition is resolved, such as renal transplant for end stage renal disease and post-partum.

The clinical course is variable. Some patients may experience only mild and infrequent symptoms not requiring regular pharmacotherapy. The severity tends to be worse with age and duration of symptoms, and inversely proportional to ferritin levels. Overall the vast majority will respond to treatment, only 5% remain refractory to treatment.

MANAGEMENT OF RESTLESS LEGS SYNDROME: CHECKLIST

- DIAGNOSIS: ESSENTIAL CRITERIA

(1) Urge to move the limbs (with or without discomfort)
(2) Begin or worse at rest or inactivity
(3) Partial or total relief with activity
(4) Worse in the evening and at night

- SUPPORTIVE CLINICAL FEATURES

(1) Positive family history
(2) Periodic limb movements in sleep
(3) Response to dopaminergic treatment

- ASSOCIATED CONDITIONS

(1) Iron deficiency: Check ferritin levels, investigate cause of iron deficiency
(2) Peripheral Neuropathy: EMG or small fibre studies if indicated
(3) Renal Failure
(4) Pregnancy

- DRUG HISTORY

Drugs which worsen RLS:
(1) Antidepressants: TCAs, SSRIs
(2) Antipsychotic agents: Neuroleptic agents, lithium
(3) Antihistamines
(4) Anti-nausea agents (metoclopramide, prochlorperazine, chlorpromazine)

- CHARACTERIZE SYMPTOMS

(1) Primary or Secondary: Treat secondary causes
(2) Intermittent or Mild symptoms: Behavioral treatment and pharmacotherapy if needed (PRN dosing, low doses)
(3) Persistent or Severe: Pharmacotherapy (Daily dosing)
(4) Painful RLS: Consider Gabapentin as 1st line, opioids if refractory

- BEHAVIOURAL TREATMENT

(1) Good sleep hygiene: Avoid poor sleep and sleep deprivation
(2) Counterstimulation (rubbing legs, hot baths, etc)
(3) Regular exercise before 7pm
(4) Reduce caffeine, tobacco and alcohol use
(5) Delay sleep and rise times

- PHARMACOTHERAPY

(1) Treat target symptom:

a. RLS symptoms (distressing urge to move): Dopaminergic agents, Opioids
b. Insomnia: Gabapentin, Benzodiazepines
c. Depression: Buproprion, Nefazodone (Avoid TCAs, SSRIs, MAOIs)
d. Pain: Gabapentin, Opioids

(2) Iron deficiency:

a. Ferrous sulfate 325mg (elemental iron 65mg) and vitamin C 200mg qd –tid (on an empty stomach) if serum ferritin < 50 mcg/L. Take 1 hour before or at least 2 hours after a meal.
b. Investigate cause of iron deficiency if indicated
c. Recheck ferritin levels in 2-3 months

(3) Timing of medication depends on onset of symptoms

a. Generally once daily at bedtime, 1-2 hours before expected time of symptom onset
b. Additional dose at dinnertime may be needed if earlier onset of symptoms
c. Daytime dose is only indicated for those with severe daytime symptoms

(4) Caution:

a. Pregnancy: Iron, folate and vitamin B12 only are safe
b. L-dopa dose should not exceed 200mg daily
c. Augmentation: Earlier or worsening symptoms
d. Intractable RLS: Review diagnosis, rule out secondary causes

- AUGMENTATION

(1) Rule out exacerbation by other factors, rebound and tolerance
(2) If on L-dopa, wean off and replace with dopamine agonist. Consider washout period. Withdrawal syndrome may occur.
(3) If already on dopamine agonist, given additional dose earlier in the day

- SUGGESTED APPROACH

	Mild RLS		
	1	2	3
Intermittent	Behavioral	L-dopa PRN	Sedative-hypnotic PRN
Persistent	Gabapentin	Dopamine agonist	Sedative-hypnotic/Opioids
	Moderate to severe RLS		
Intermittent	L-dopa PRN	Sedative-hypnotic PRN	Opioids PRN
Persistent	Dopamine agonist	Gabapentin	Sedative-hypnotic/Opioids
Painful RLS	Gabapentin	Opioids	Dopamine agonist

RLS drugs		
Dose Range(mg)	T ½ (hours)	Side Effects

Anticonvulsants			
Gabapentin	100-2700 (max. 1200mg/dose)	5-7	Sedation, dizziness, ataxia
Dopaminergic agents			
L-dopa (CR)	50-200	1.5-2 (6-8)	Nausea, vomiting, orthostatic hypotension, insomnia, hallucinations, augmentation
Pergolide (Permax)*	0.025-0.5	12-16	
Pramipexole (Mirapex)*	0.125-1.5	8-10	
Ropinirole (Requip)*	0.25-3.0	6-8	
Sedative-Hypnotics			
Zaleplon (Sonata) Zolpidem (Ambien)	5-20 5-20	1 1.6	Sedation, respiratory depression, tolerance, dependence
Clonazepam (Klonopin)	0.25-2.0	30-40	
Opioids			
Codeine	15-120	2-3	Sedation, constipation, nausea, vomiting, pruritis, dry mouth, dependence
Oxycodone (OxyContin)	5-30	3	
Hydrocodone	5-30	3	
Tramadol (Ultram)	50-300	5-8	
Propoxyphene (Darvon-N)	100-600	6-12	
Methadone	2.5-20	16-22	

*Instructions for patients: Pergolide 0.05mg or Pramipexole 0.25mg or Ropinirole 0.25mg:

Take ½ tablet 2 hours before bedtime. Increase to 1 tablet after 3 days if no side effects or benefit. Continue to increase by ½ tablet every 3 days until there is benefit or side effects develop.

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