Restless leg syndrome, periodic limb movements, febrile seizures and Attention deficit hyperactivity disorder in an Indian family

Meena Gupta, Amit Batra, Anurag Trivedi, Debashish Chowdhury, Geeta A. Khwaja

Department of Neurology, GB Pant Hospital, JLN Marg, New Delhi, India

Abstract

Restless leg syndrome (RLS) is a common neurological disorder which can affect individuals of all age groups and incidence increasing with age. It can cause severe sleep disruption and negatively impact quality of life of an individual. Its diagnosis is clinical, based on essential criteria of International RLS Study Group. It can be idiopathic or associated with various medical and other neurological disorders. Idiopathic RLS can be sporadic or may have a familial inheritance, with several genetic loci been reported till date. RLS has a strong association with periodic limb movements, both sleep and awake. Very few studies of familial RLS/Periodic limb movements in sleep and their associations have been reported. We report an Indian family with autosomal dominant RLS/PLMS, with RLS and PLMS as well as psychiatric disorders, febrile seizures and Attention Deficit Hyperactivity Disorder in different family members, over three generations.

Key Words

Familial, periodic limb movements, restless leg syndrome

For correspondence:

Dr. Meena Gupta, Department of Neurology, 5th Floor, Academic Block, GB Pant Hospital, JLN Marg, New Delhi-110 002, India. E-mail: drmeenagupta@gmail.com

Ann Indian Acad Neurol 2012;15:39-43

Introduction

Restless leg syndrome (RLS) is a disorder of combined sensory and motor dysfunction first described by Swedish neurologist Ekbom in 1945.[1] It is characterized by an urge to move the legs, usually accompanied by uncomfortable sensations in the limbs. The sensations usually are worse during inactivity and often interfere with sleep, leading to walking discomfort, chronic sleep deprivation, and stress.[2]

Epidemiological studies suggest that prevalence of RLS in the general population is between 1.2 and 15%.[3,4] It is twice as common in females in comparison with males.[5] RLS may be idiopathic or may be secondary when associated with other conditions like iron deficiency, low serum ferritin levels, pregnancy, end-stage renal disease, diabetes mellitus, and rheumatoid arthritis.[6-8] Some neurological disorders are also related to RLS, like spinocerebellar atrophy, peripheral neuropathy, spinal canal stenosis, lumbo-sacral radiculopathy, myelopathy, and Parkinson's disease.[9,10] In children, RLS is associated with attention deficit hyperactivity disorder.[11-13]

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.93277

The diagnosis of RLS is made clinically on the basis of the following 4 essential criteria:

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting.
- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

There are additional features that support a diagnosis of RLS, like presence of family history of RLS, periodic leg movements, response to dopaminergic therapy, sleep disturbance, and no abnormality in medical and physical evaluation.[14]

Idiopathic RLS appears to run in families, suggesting a genetic basis for the disorder.[15,16] Twin studies have been consistent in showing that RLS has a genetic etiology.[17,18] Several loci for RLS have been reported. These include one autosomal recessive

locus in a French-Canadian pedigree and four autosomal dominant loci in a North Italian pedigree, one each from the United States, South Tyrol, and large French–Canadian pedigree.

Nearly 80% of people with RLS have Periodic Limb Movements in sleep (PLMS) or awake state.[19] These are involuntary repetitive segmental movements of the lower and/or upper limbs, consisting of flexion of the thighs, knees, ankles, and big toe with fanning of the small toes, occurring in sleep or awake state.[20] A higher incidence of PLMS has also been found in asymptomatic first-degree relatives of early onset RLS subjects. PLM may also be associated with narcolepsy, sleep apnea syndrome, REM sleep behavior disorder, and normal elderly subjects. PLMS during wakefulness has been recognized as a sensitive and specific RLS marker.[21]

Presently, no family studies of RLS/PLMS or their associates are available from the Indian subcontinent. We describe a family with autosomal dominant RLS/PLMS and report their clinical details, associations and investigative data including serum ferritin and polysomnography.

Materials and Methods

Our proband, 65 years old male, presented with complaints of pain in both lower limbs in the evening and night, urge to move the legs and relieved by walking, along with rapid jerky movements of limbs for more than 25 years. These movements used to occur both in awake state as well as in sleep, causing severe sleep disruption. These were more common during periods of rest, after activity and never occurred during action or movement and were relieved on walking. Occasionally while sitting, because of these movements, patient had a tendency to lose his balance. Clinical history suggested diagnosis of RLS with PLMs (sleep and awake). Family history revealed similar complaints suggestive of (RLS and / PLMS) and some neuropsychiatric disorders in his daughters, sons, and grandchildren. Family tree is shown in Figure 1.

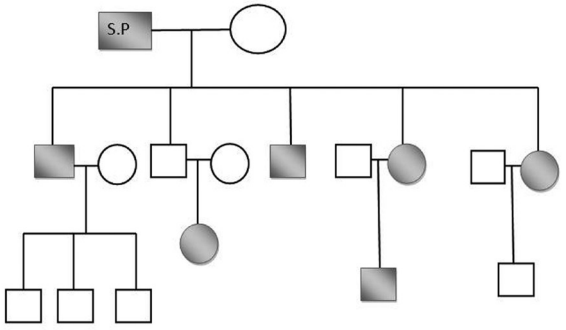

Figure 1: Familytree

Besides the clinical examination, the Index case and 8 family members underwent all routine investigations along with serum ferritin levels and an overnight supervised polysomnography (PSG) at our sleep laboratory. The diagnoses of RLS and PLMS were based on the standard international criteria.[14]

Observation

Hemogram, renal and liver functions were normal. Serum ferritin levels were below normal in the proband and his two daughters and affected grandson. Nerve conduction studies were normal. The index case had PLM in sleep, rapid and jerky in nature, occurring very frequently every few seconds throughout the night, predominantly involving both lower limbs, with frequent awakenings causing severe sleep disruption. The associated symptoms of RLS, no Electroencephalography (EEG) correlate, occurrence only during rest, and subsequent dramatic improvement with pramipexole ruled out the possibility of these movements being myoclonus. Five other family members were also found to have PLM in sleep, PLMS index ranging from 16 to 30/hr, more in the first 3 to 4 hours of sleep and stages 1 and 2 of Non Rapid Eye Movement (NREM)sleep. One of these family members was unaware of these movements. All 3 (100%) subjects with RLS had PLMS, while only 50% of patients with PLMS fulfilled the criteria for RLS [Table 1]. The index case was started on treatment with Dopa agonist (pramipexole) and he had relief in his symptoms of RLS as well as marked reduction in the leg movements [Figures 2 and 3]. Treatment was also started for his daughters and grandson. Benzodiazepine (clonazepam) was started for young daughter. Benzodiazepines (clonazepam) with pramipexole were given to elder daughter and Levodopa to grandson who had attention deficit hyperactivity disorder (ADHD) along with PLMS. Both daughters and grandson had marked relief in their symptoms.

Table 1: Clinical attributes of family members

Subject	RLS	PLMS	PLM awake	Febrile seizures	Psychiatric disorders	ADHD	Serum ferritin levels (ng/ml)
Index case	Yes	Yes	Yes	-		-	
Son (37 years)	-	Yes	-	Yes	-	-	36.44
Son (27 years)	-	-	-			-	117.0
Son (25 years)	-	-	-	-	Anxiety		52.28
Daughter (30 years)	Yes	Yes	Yes	Yes	Depression	-	23.0
Daughter (23 years)	Yes	Yes	-	-	-	-	
Grandson (10 years)	-	Yes	-	Yes	-	Yes	28.7
Grand-daughter (2 years)	-	Yes	-	-	-	-	

RLS = Restless leg syndrome; PLM = Periodic limb movements; ADHD = Attention deficit hyperactivity disorder; PLMS = Periodic limb movements in sleep

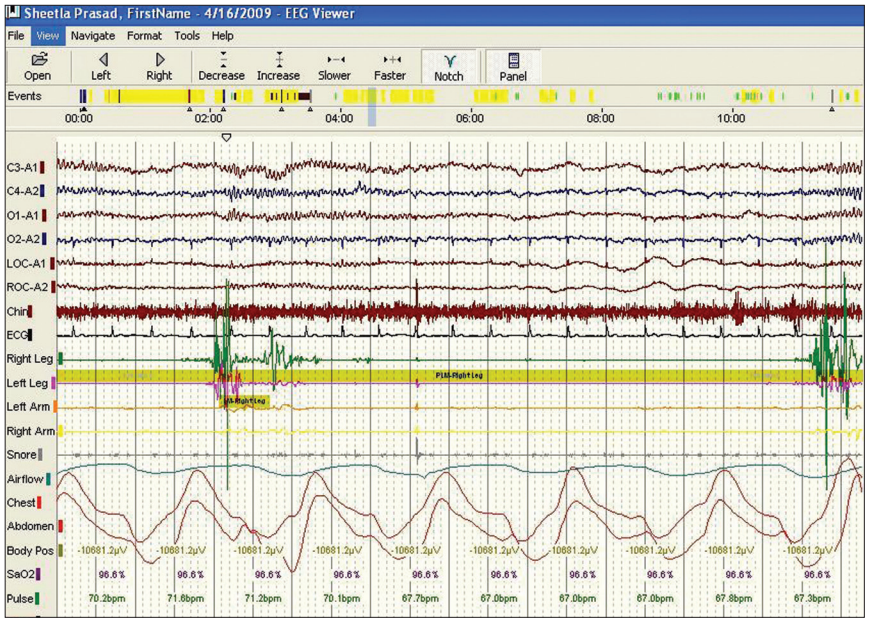

Figure 2: Pretreatment polysomnography overview of the index case

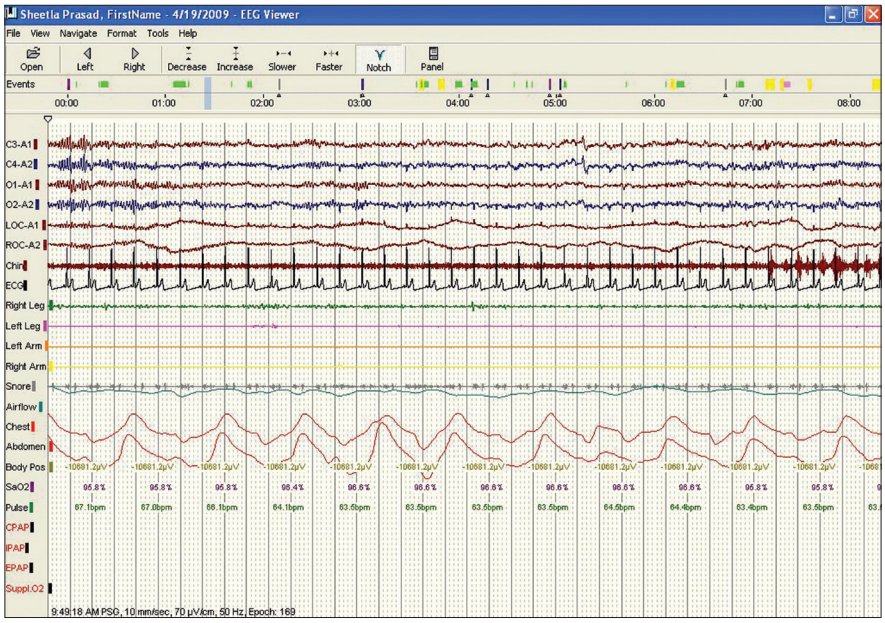

Figure 3: Post-treatment polysomnography overview of the index case

Discussion

RLS and PLMS are relatively common sleep problems with limited descriptions from India[22,23] The impairment of dopaminergic transmission (involvement of D3 subtype receptors) and iron metabolism is supposed to be involved in the pathogenesis of RLS and PLMS. There are several studies showing relation between dopaminergic system and RLS.[24,25] A low serum ferritin level (less than 50 µg/l) has been associated with greater severity of RLS, more frequent PLM, and with a reduction in the quantity of sleep, as determined by PSG.[26] The iron containing enzyme, tyrosine hydroxylase, catalyzes the hydroxylation of tyrosine to dihydroxyphenylalanine (levodopa) which is carboxylated to form dopamine. Iron is therefore a rate limiting step in the formation of dopamine. RLS and PLMD might be induced by inhibition of dopamine formation through lack of iron.[27] In patients with a serum ferritin level of less than 18 µg/l, treatment with oral iron supplements resulted in improvements in the severity of the symptoms of RLS and, in some patients, the complete resolution of the symptoms.[28] A 68% decrease in cerebrospinal fluid (CSF) ferritin and a greater than three-fold increase in CSF transferrin, indicative of low brain iron, have been reported in patients with idiopathic RLS.[29] Allen *et al* also demonstrated lower iron concentrations in the substantia nigra and putamen in proportion to severity of symptoms in RLS patients compared with controls.[30] We have also found decreased serum ferritin levels in index case and family members who had RLS/PLMS.

Family history of RLS is positive in nearly 50% of patients with idiopathic RLS.[31] Familial cases have a younger age at onset[32] and a more slowly progressive course,[33] as seen in our case and his family members. Linkage studies in RLS families have revealed several loci including chromosome 12q, 14q, 9p, 20p, 2q, 16p.[34] Genetic studies could not be done in our case due to lack of defined genetic loci and financial constraints in our set up, which is a limitation of the study.

RLS/PLMS occur in a higher percentage of children with ADHD. [11-13] In the described family, one grandson with PLMS also had history of ADHD and was started on treatment with levodopa. The pathogenesis of this association includes genetic linkage, common dopaminergic deficit, or sleep disruption. Treatment with levodopa/dopamine agonist is effective in improving symptoms of both.[35] Our patient also had significant improvement not only in PLMS, but also in ADHD, resulting in betterment of his scholastic performance.

Neuropsychiatric disorders like major depression, anxiety, and panic disorder have also been strongly associated with RLS/PLMS.[36-38] The explanations include common pathophysiological mechanism of dopaminergic deficiency, insomnia, and use of antidepressants. RLS being a highly familial disorder, the increased risk of specific depressive and anxiety disorders could have a genetic etiology as well.[39] Two of the family members in the study had history of psychiatric disorder (anxiety/depression).

Treatment of RLS includes avoidance of drugs which can worsen or precipitate RLS/PLM, e.g, selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine, sertraline), venlaflaxine, antihistaminics, and caffeine, correction of iron deficiency, and management of underlying condition like uremia. Drug therapy includes the following three major classes of drugs: dopaminergic agents (levodopa, bromocriptine, pergolide, and pramipexole), opioids (propoxyphene, oxycodone, methadone), and benzodiazepines (clonazepam, nitrazepam, triazolam). Other pharmacological agents which have been evaluated in various studies for subjective improvement in RLS symptoms include carbamazepine, valproic acid, gabapentin, and baclofen. Dopaminergic drugs are however considered the first line of management of idiopathic RLS.[40]

Thus, we report a unique Indian family with RLS, PLMS, febrile seizures, psychiatric disorders, and ADHD in family members. A detailed history of these associations in family members of patients with RLS/PLMS should hence be carefully sought. Early recognition and treatment of these disorders and their correlates can markedly improve the quality of life in these patients.

References

1. Ekbom KA. Restless legs: A clinical study. Acta Med Scand 1945;158:1-123.
2. Silber MH. Restless legs syndrome. Mayo Clin Proc 1997; 72:261-4.
3. 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.
4. Mata IF, Bodkin CL, Adler CH, Lin SC, Uitti RJ, Farrer MJ, *et al*. Genetics of restless legs syndrome. Parkinsonism Relat Disord 2006;12:1-7.
5. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004;164:196-202.
6. Takaki J, Nishi T, Nangaku M, Shimoyama H, Inada T, Matsuyama N, *et al*. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. Am J Kidney Dis 2003;41:833-9.
7. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, *et al*. Restless legs syndrome and pregnancy. Neurology 2004;63:1065-9.
8. Matthews WB. Iron deficiency and restless legs. Br Med J 1976;1:898.
9. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol 2002;59:421-4.
10. Walters AS, Wagner M, Hening WA. Periodic limb movements as the initial manifestation of restless legs syndrome triggered by lumbosacral radiculopathy. Sleep 1996;19:825-6.
11. Konofal E, Cortese S, Marchand M, Mouren MC, Arnulf I, Lecendreux M. Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. Sleep Med 2007;8:711-5.
12. Oner P, Dirik EB, Taner Y, Caykoylu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med 2007;213:269-76.
13. Cortese S, Konofal E, Lecendreux M, Arnulf I, Mouren MC, Darra F, *et al*. Restless legs syndrome and attention-deficit/hyperactivity disorder: A review of the literature. Sleep 2005;28:1007-13.
14. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. 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.
15. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61-5.
16. Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47:1435-41.
17. Ondo WG, Vuong KD, Wang Q. Restless legs syndrome in monozygotic twins: Clinical correlates. Neurology 2000;55:1404-6.
18. Desai AV, Cherkas LF, Spector TD, Williams AJ. Genetic influences in self-reported symptoms of obstructive sleep apnoea and restless legs: A twin study. Twin Res 2004;7:589-95.
19. Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-dopa. Sleep 1996;19:196-9.
20. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. Sleep Med Rev 2006;10:169-77.
21. Michaud M, Paquet J, Lavigne G, Desautels A, Montplaisir J. Sleep laboratory diagnosis of restless leg syndrome. Eur Neurol 2002;48:108-13.
22. 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;4:143-6.
23. Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: A case-controlled study. Mov Disord 2003;18:181-5.
24. Turjanski N, Lees AJ, Brooks. DJ Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 1999;52:932-7.
25. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J

Neurol 2002;249:164-70.
26. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing 1994;23:200-3.
27. Earley C. Word from the doctors: The importance of iron in restless legs syndrome. United States: The Night Walkers Newsletter; 1997.
28. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep 1998;21:371-7.
29. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54:1698-700.
30. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001;56:263-5.
31. Holmes R, Tluk S, Metta V, Patel P, Rao R, Williams A, *et al*. Nature and variants of idiopathic restless leg syndrome: Observations from 152 patients referred to secondary care in the UK. J Neural Transm 2007;114:929-34.
32. Winkelmann J. The genetics of restless legs syndrome. Sleep Med 2002;3:S9-12.
33. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome using age-of-symptom-onset. Sleep Med 2000;1:11-9.
34. Trotti LM, Bhadriraju S, Rye DB. An update on the pathophysiology and genetics of restless legs syndrome. Curr Neurol Neurosci Rep 2008;8:281-7.
35. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, *et al*. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord 1999;14:1000-7.
36. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: The MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000;54:1064-8.
37. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000;160:2137-41.
38. Saletu M, Anderer P, Saletu B, Lindeck-Pozza L, Hauer C, Saletu-Zyhlarz G. EEG mapping in patients with restless legs syndrome as compared with normal controls. Psychiatry Res 2002;115:49-61.
39. Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, *et al*. Clinical characteristics and frequency of hereditary restless legs syndrome in a population of 300 patients. Sleep 2000;23:597-602.
40. Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder: An American Academy of Sleep Medicine review. Sleep 1999;22:970-99.

How to cite this article: Gupta M, Batra A, Trivedi A, Chowdhury D, Khwaja GA. Restless leg syndrome, periodic limb movements, febrile seizures and Attention deficit hyperactivity disorder in an Indian family. Ann Indian Acad Neurol 2012;15:39-43.

Received: 18-08-10, **Revised:** 20-10-10, **Accepted:** 03-12-10

Source of Support: Nil, **Conflict of Interest:** Nil