

Editorial

## Editor's corner: restless legs syndrome, a common disease uncommonly diagnosed

This special issue is devoted to restless legs syndrome (RLS), a disease prevalent in the general population, but often misdiagnosed, underdiagnosed or undiagnosed. Although the entity was mentioned in English literature by Thomas Willis [1] in 1685, it was not until Ekbom's lucid description [2] in 1945, under the heading 'Restless legs: a clinical study', that the scientific community became aware of this condition. Fifty years after Ekbom's prophetic remarks, the International RLS Study Group (IRLSSG) established a set of diagnostic criteria [3]. This was the beginning of a fruitful research in epidemiology, genetics, pathophysiology and therapy of RLS.

Frequent misdiagnosis and poor recognition have hampered epidemiologic studies in RLS. A case in point is the recent survey from Europe and the USA showing correct diagnosis of RLS by general physicians to be less than 7% of cases diagnosed by specialists based on the IRLSSG criteria [4]. Although Wittmaack [5] described RLS-like symptoms under the heading of 'Anxietas tibiae,' almost a century and a half ago, at the beginning of the 21st century, patients are still misdiagnosed as suffering from anxiety or other psychological disorders. There has been a wide variation from 1 to 15% in the estimated prevalence of RLS. Ekbom's original study quoted 5%, but modern studies, particularly from North America and Europe, have given an approximate prevalence of 10% [6–11]. The extremely low prevalence in the studies from Singapore, Japan and India [12–14] (see the article by Bhowmik et al. in this issue) suggests possible racial or ethnic factors in its occurrence.

Genetic predisposition has been suggested in primary or idiopathic RLS, and perhaps even in the secondary RLS associated with a variety of disorders, particularly iron deficiency anemia, uremia and polyneuropathy. An increased incidence of RLS is noted in the first-degree relatives [15]. It has been suggested that there may be two different phenotypes for this disorder based on family history, age of onset and progression of the disease [16]. A study showing high concordance in monozygotic twins [17] and the study from Germany [18] suggested an autosomal dominant inheritance. In a recent linkage study involving a large French–Canadian family, the susceptibility locus was

found to be on the short arm of chromosome 12 and the inheritance was thought to be autosomal recessive in nature [19].

Recent research into the pathophysiology of RLS revolves around electrophysiologic, pharmacologic and neuroimaging findings. The first clue to the currently presumed dopaminergic deficiency theory of RLS came from Akpinar's letter to the Editor in 1982 showing improvement of RLS symptoms after levodopa ingestion [20]. Pharmacologic and neuroimaging studies and clinical drug trials [21–24] subsequently provided indirect evidence of dopaminergic abnormality in RLS. Akpinar's brief report also opened therapeutic avenues for alleviating RLS symptoms. Although some positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have suggested mild but significant pre- and postsynaptic dopamine receptor abnormalities in the basal ganglia [25–28], there are other dopamine system imaging studies contradicting these findings [29,30]. Similarly, some electrophysiologic and functional magnetic resonance imaging (MRI) studies [31–33] have suggested a possible site of abnormality in the brainstem, but negative blink reflex excitability studies [34] (and also personal unpublished observations) contradict this observation. Magnetic brain stimulation studies suggest cortical hyperexcitability as a result of subcortical dysfunction [35,36]. In contrast, studies of the spinal flexor reflex in both idiopathic and secondary RLS associated with chronic renal failure point to a possible spinal cord dysfunction, probably as a result of disinhibition from the brainstem [37,38].

The most exciting current development in RLS research involves brain iron depletion as a cause of dopamine abnormality [39,40]. As early as 1945, Ekbom [2] suggested iron deficiency in RLS, and Norlander in 1953 and 1954 [41, 42] reported the usefulness of intravenous iron treatment for this condition. However, the iron deficiency theory took a giant leap forward when O'Keefe et al. [43] revisited the question of iron status in RLS in 1994. Iron is needed for dopamine synthesis and formation, and its deficiency may impair the normal production of dopamine. There is a circadian rhythm for both iron and dopamine production, with the lowest levels at night when RLS symptoms are

exacerbated. Low iron stores measured by ferritin levels have been noted in many elderly subjects who are often relieved of RLS symptoms by both iron and dopamine [39]. Individuals with iron deficiency anemia, uremia and pregnancy often have low iron stores predisposing them to secondary RLS. These pharmacologic facts compliment recent imaging studies showing striatal dopamine abnormalities.

Many questions, however, remain unresolved, particularly why brain iron depletion occurs in RLS patients and which dopaminergic pathway (nigrostriatal or non-nigrostriatal) is involved in dopamine depletion and the positive therapeutic response to dopaminergic agents.

There has been a concerted effort recently to educate both the professionals and the public about the existence of RLS, probably the most common movement disorder in our practice and one of the frequent sleep disorders in the day-to-day practice of sleep medicine. The Restless Legs Syndrome Foundation, International RLS Study Group, National Sleep Foundation, National Center on Sleep Disorders Research within the National Institutes of Health, and the Sleep Section of the American Academy of Neurology have taken leadership roles in such education. The editorial board of 'Sleep Medicine' recently concluded that this is an opportune moment to bring out a special issue on this common but uncommonly diagnosed entity. In this issue, special emphasis has been placed on articles dealing with validation of the IRLSSG rating scale and the consensus of the recently concluded workshop at the NIH dealing with revised diagnostic criteria for RLS and its epidemiology, as well as RLS in the elderly and children. The issue also includes articles on factor analysis of the IRLSSG scale for RLS severity and preliminary investigations for the validation of the Johns Hopkins telephone diagnostic interview for RLS in a multicenter population. The last three articles deal with RLS in hemodialysis patients from India, different sleep characteristics in RLS and periodic limb movement disorder, and development of RLS in a patient with periodic limb movements following dopaminergic treatment. In addition to this editor's corner, there is an editorial emphasizing the continuing development of diagnostic standards and severity measures for RLS. A second editorial addresses the reliability of the validation process of a telephone diagnostic interview questionnaire (see the article by Hening et al. in this issue.) Finally, the Journal Search and Commentary section for this issue most appropriately focuses on RLS-related articles.

We, in the editorial office, hope that this special issue will stimulate further research and clinical trials deepening our understanding of the pathophysiology and expanding the therapeutic options for the unfortunate individuals suffering from this distressing disorder. I would like to thank the contributors and Elsevier Publishing Company for helping us bring out this special issue 58 years after Ekbom's authoritative description of a common but often misunderstood entity rightfully also known as Ekbom syndrome.

## References

- [1] Willis T. The London practice of physic. London: Thomas Basset and William Crook, 1685.
- [2] Ekbom KA. Restless legs: a clinical study. *Acta Med Scand* 1945; 158(Suppl):1–123.
- [3] The International Restless Legs Syndrome Study Group. Toward a better definition of the restless legs syndrome. *Mov Disord* 1995;10: 634–42.
- [4] Allen R, Hening W, Montplaisir J, et al. Restless legs syndrome (RLS), a common disorder rarely diagnosed in Europe or USA: the REST (RLS epidemiology, symptoms and treatment) study in primary care (Abstract). *Mov Disord* 2002;17:S240.
- [5] Wittmaack T. *Lehrbuch der Nervenkrankheiten. I. Pathologic and Therapie der Sensibilitat-Neuro-sen.* Leipzig: E. Schafer, 1861.
- [6] Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and associations among Canadians. *Sleep* 1994;17:739.
- [7] Johnson ED. *Omnibus sleep in America poll.* Washington, DC: National Sleep Foundation, 2000.
- [8] Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. *Arch Intern Med* 2000;160:2137.
- [9] Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population; the MEMO study. Memory and morbidity in Augsburg elderly. *Neurology* 2000;54:1064–8.
- [10] Miranda M, Araya F, Castillo JL, et al. Restless legs syndrome: a clinical study in adult general population and in uremic patients. *Rev Med Chil* 2001;129:179–86.
- [11] Ulfberg J, Nystrom B, Carter N, Edling C. Restless legs syndrome among working-aged women. *Eur Neurol* 2001;46:17–19.
- [12] Tan EK, Seah A, See SJ, et al. Restless legs syndrome in an Asian population: a study in Singapore. *Mov Disord* 2001;16:577–9.
- [13] Inoue Y, Ishizuka T, Arai H. Surveillance on epidemiology and treatment of restless legs syndrome in Japan. *J New Rem Clin* 2000; 49:244–54.
- [14] Bhowmik D, Bhatia M, Gupta S, et al. Restless legs syndrome in hemodialysis patients in India: a case controlled study. *Sleep Med* 2003;4:53–56.
- [15] Hening WA, Washburn T, Allen RP, Earley C. A family study of RLS: presence of an elevated prevalence of affected first and second degree relatives. *Neurology* 2002;58(Suppl 3):A513–4.
- [16] Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. *Sleep Med* 2000;1: 11–19.
- [17] Ondo WG, Vuong KD, Wang Q. Restless leg syndrome in monozygotic twins: clinical correlates. *Neurology* 2000;55:1404–6.
- [18] Winkelmann J, Muller-Myhsok B, Wittchen HU, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance. *Ann Neurol* 2002;52: 297–302.
- [19] Desautels A, Turecki G, Montplaisir J, et al. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet* 2001;69:1266–70.
- [20] Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide (letter). *Arch Neurol* 1982;39:739.
- [21] Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double blind randomized trial. *Neurology* 1999;52:938–43.
- [22] Wetter TC, Stiasny K, Winkelmann J, et al. A randomized, controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999;52:944–50.
- [23] Staedt J, Wabmuth F, Ziemann U, et al. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-dopa. *J Neural Transm* 1997;104:461–8.
- [24] Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-

- controlled trial of pergolide in restless legs syndrome. *Neurology* 1998;51:1599–602.
- [25] Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic receptor dysfunction in restless legs syndrome:  $^{18}\text{F}$ -dopa and  $^{11}\text{C}$ -raclopride PET studies. *Neurology* 1999;52:932–7.
- [26] Ruottinen HM, Partinen M, Hublin C, et al. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. *Neurology* 2000;54:502–4.
- [27] Staedt J, Stoppe G, Kogler A, et al. Single photon emission tomography (SPET) imaging of dopamine D2 receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome (NMS). *J Neural Transm* 1995;99:187–93.
- [28] Michaud M, Soucy JP, Chabli A, et al. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic limb movements in sleep. *J Neurol* 2002;249:164–70.
- [29] Trenkwalder C, Walters AS, Hening WA, et al. Positron emission tomographic studies in restless legs syndrome. *Mov Disord* 1999;14:141–5.
- [30] Eisensehr I, Wetter TC, Linke R, et al. Normal IPT and IBZM SPECT in drug-naïve and levodopa-treated idiopathic restless legs syndrome. *Neurology* 2001;57:1307–9.
- [31] Briellmann RS, Rosler KM, Hess CW. Blink reflex excitability is abnormal in patients with periodic leg movements in sleep. *Mov Disord* 1996;11:710–4.
- [32] Wechsler LR, Stakes JW, Shahani BT, Busis NA. Periodic leg movements of sleep (nocturnal myoclonus): an electrophysiological study. *Ann Neurol* 1986;19:168–73.
- [33] Bucher SF, Seelos KC, Oertel WH, et al. Cerebral generators involved in the pathogenesis of restless legs syndrome. *Ann Neurol* 1997;41:639–45.
- [34] Bucher S, Trenkwalder C, Oertel W. Reflex studies and MRI in the restless legs syndrome. *Acta Neurol Scand* 1996;94:145–50.
- [35] Tergau F, Wischer S, Paulus W. Motor system excitability in patients with restless legs syndrome. *Neurology* 1999;52:1060–3.
- [36] Entezari-Taher M, Singleton JR, Jones CR, et al. Changes in excitability of motor cortical circuitry in primary restless legs syndrome. *Neurology* 1999;53:1201–5.
- [37] Bara-Jimenez W, Aksu M, Graham B, et al. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. *Neurology* 2000;54:1609–16.
- [38] Aksu M, Bara-Jimenez W. State dependent excitability changes of spinal flexor reflex in patients with restless legs syndrome secondary to chronic renal failure. *Sleep Med* 2002;3:427–30.
- [39] Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and psychophysiological features. *J Clin Neurophysiol* 2001;18:128–47.
- [40] Chokroverty S, Jankovic J. Restless legs syndrome: a disease in search of identity. An editorial. *Neurology* 1999;52:907–10.
- [41] Norlander NB. Therapy in restless legs. *Acta Med Scand* 1953;145:453–7.
- [42] Norlander NB. Restless legs. *Br J Phys Med* 1954;17:160–2.
- [43] O’Keefe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing* 1994;23(3):200–3.

Sudhansu Chokroverty\*

*Saint Vincents Hospital and Medical Center, 153 West 11th  
St. Cronin 466  
New York, NY 10011, USA*

---

\* Corresponding author. Tel.: +1-212-604-2401; fax: 1-212-604-1555.  
E-mail address: schok@worldnet.att.net (S. Chokroverty).