

RESTLESS LEGS SYNDROME

LUIGI RAMPOLLO*, IGNAZIO VECCHIO**, MICHELE MALAGUARNERA***, LIBORIO RAMPOLLO*

*"G.F. Ingrassia" Department, Neurosciences Unit, University of Catania, Azienda Policlinico Vittorio Emanuele, **Department of Medical and Pediatric Sciences, ***Department of Biological Chemistry, Medical Chemistry and Molecular Biology, University of Catania

[Sindrome delle gambe senza riposo]

ABSTRACT

This paper describes the restless legs syndrome and the typical symptoms associated with clinical variants. It also describes the epidemiology, etiological hypotheses, and differential diagnosis with other involuntary movements of the limbs. Possible risk factors and potential drug treatments are then proposed.

Key words: Restless legs syndrome (RLS), sleep disorders, periodic limb movements in sleep (PLMS), insomnia

Received August 29, 2012; Accepted September 12, 2012

Introduction and symptoms

The "restless leg syndrome" is an unclear pathological condition that affects a large percentage of the general population, which can even reach 2-10%, without prevalence of sex, with possible effects on both the daytime efficiency of the people affected and the quality of sleep, with obvious repercussions on the daytime performance.

It is a medical condition that is more frequently reported by healthy adults with an evolutionary trend that at times can also lead to an involvement of the upper limbs.

The epidemiology lacks an adequate knowledge of the disease that is not easily recognized or rather is easily mistaken for anxiety, depression, and arthritis⁽¹⁾.

It is described, at least initially, as a bothersome feeling of restlessness arising in particular in conditions of immobility, and specifically at the time of going to bed for nighttime rest: patients feel an irresistible urge to move their legs to escape the intolerable feeling variously described as tingling, stretching, muscle tension, stiffness, motor impermissibility located below the knees. The consequence

is the systematic need of having to get up to ease, albeit temporarily, the unpleasant feelings through movement. Upon returning to bed, the phenomenon tends to recur. The more stubborn and prolonged it is, the more chronic the onset of the disease⁽²⁾.

Known also as "anxietas tibiaram", it is not easy to date its first description. It is not a recent condition, which, if left untreated, can also be debilitating at times (see Table 1).

<i>1. Unpleasant sensations in the lower limbs or difficulty to fall asleep</i>
<i>2. Unpleasant sensations of trembling in the calves, often associated with tenderness or generalized pain in the lower limbs</i>
<i>3. The disorders are relieved by moving the limbs</i>
<i>4. Polysomnographic monitoring shows the presence of movements of the limbs at rest</i>
<i>5. No medical or mental pathologies that may account for the symptoms</i>
<i>6. There may be other sleep disorders but they are not responsible for the symptoms</i>

Table 1: Diagnostic criteria for the diagnosis of restless legs syndrome.

It is a typically circadian pathology with a prevalence in the last hours of the day and the early hours of the next: hence the tendency of patients who are aware of it to fall sleep later and later to avoid the disturbance by sleeping at different hours.

It is not difficult to distinguish it from the more common feeling of muscle soreness associated with intense physical activity carried out during the day, as it tends to easily and spontaneously disappear in a few days, without resorting to any drug treatment⁽³⁾.

However, distinguishing it from other similar conditions that may mimic the restless legs syndrome is more complex.

In the absence of treatment or resistance to the therapy provided, as time goes by, the symptoms may occur at times even during the day in the absence of rest or immobility, which are considered the triggers in the initial phase of the disease; in severe cases the restless legs syndrome may become incompatible with sitting or reclining (driving, travel, sleep).

The aggravating factors include physical fatigue and higher room temperatures.

Etiopathogenesis

In the absence of clear knowledge on the etiopathogenesis of the disease, vascular, systemic, genetic, and neurogenic (central and peripheral) causes have been suspected. Some argue for a myelopathic disorder. Smoking, obesity, physical inactivity, diabetes, and the intake of tricyclics, serotonin, and antidopaminergic drugs have been considered predisposing factors⁽⁴⁾.

Differential diagnosis

To date, the etiopathogenesis is not defined. It may represent the onset of peripheral neuropathy, especially due to advanced stage chronic renal failure. However, several clinical conditions have been associated with restless legs syndrome, such as iron deficiency anemia, folate deficiency, pregnancy, thyroid disease, hyperferritinemia, the use of antidepressants or antihistamines: these associations offer little help to understand the origin of the disease.

It is not difficult to differentiate the restless legs syndrome from periodic leg movements in sleep (once inappropriately called nocturnal myoclonus, as in this case myoclonic movements

are notoriously more rapid compared to periodic nocturnal movements) (International Restless Legs Study Group (IRLSSG)). These are involuntary, periodical, slow, sleep-related movements involving dorsiflexion of the foot and knee and hip flexion, which occur in the complete absence of conscience and will of the subject who, however, can interrupt sleep at such moments (sometimes repeatedly during the same night, with the well-known effects on daytime performance) (see Table 2).

<i>1. Insomnia or excessive drowsiness; at times the patient is not aware of the presence of the disorder, but the movements are observed by others</i>
<i>2. Repetitive and highly stereotyped movements of the lower limbs</i>
<i>3. Polysomnographic monitoring shows:</i> <ul style="list-style-type: none"> • <i>Repeated episodes of contractions (every 20-40 seconds)</i> • <i>Associated episodes of awakening</i>
<i>4. No medical or mental pathologies that may account for the symptoms</i>
<i>5. There may be other sleep disorders but they are not responsible for the symptoms</i>

Table 2: Diagnostic criteria for the diagnosis of periodic limb movement syndrome.

The latter may be associated with the restless legs syndrome (30% of cases), which sometimes makes it daunting to distinguish the two conditions without the use of polysomnography, as well as with the intake of tricyclic antidepressants, serotonin, and L-Dopa or with discontinuation of antiepileptic drugs or sedatives⁽⁵⁾.

Therapeutic orientations

In the absence of a clear etiopathogenesis, several therapeutic proposals have been made: dopaminergic agents, opioids, anticonvulsants, benzodiazepines, clonidine, propranolol, and baclofen.

With the exclusion of dopaminergic ergolines now suspended from use due to the known effects on the heart and in terms of pulmonary and retroperitoneal sclerosis, the most recurrent option today appears to be the use of a low-dose synthetic dopaminergic agent or slow-release levodopa formulations to avoid rebound effects. Among benzodiazepines, the preference goes to clonazepam whose effect is difficult though to assess in terms of direct effects on the cause of the disease or conse-

quential effects on induction and maintenance of sleep. The use of gabapentin should be reserved for cases with a neuropathic component⁽⁶⁾. There has been recent clinical and experimental evidence supporting the possibility of a beneficial effect of L-acetyl-carnitine⁽⁷⁻⁹⁾.

References

- 1) Philips B et al. *Epidemiology of restless legs syndrome in adults*. Arch. Intern. Med. 160: 137, 2000.
- 2) Walter AS. *Toward a better definition of the restless legs syndrome*. International Restless legs syndrome Study Group. Mov. Disord. 10: 634, 1995.
- 3) Berger K, Kurth T. *RLS epidemiology, frequencies, risk factors and methods in population studies*. Mov Disord 2007; 22 (Suppl 18): S420-3.
- 4) Earley CJ *Restless legs syndrome*: N. Eng. J. Med 348:2103 2003
- 5) Ohayon MM, Roth T. *Prevalence of restless legs syndrome and periodic limb movement disorder in the general population*. J Psychosom Res 2002; 53: 547 e 54.
- 6) Paulus W, Dowling P, Rijsman R, et al. *Pathophysiological concepts of restless legs syndrome*. Mov Disord 2007; 22: 1451-6.
- 7) Malaguarnera M, Vacante M, Giordano M, Pennisi G, Bella R, Rampello L, Malaguarnera M, Li Volti G, Galvano F. *Oral acetyl-L-carnitine therapy reduces fatigue in overt hepatic encephalopathy: a randomized, double-blind, placebo-controlled study*. Am J Clin Nutr. 2011 Apr; 93(4): 799-808.
- 8) Malaguarnera M, Vacante M, Motta M, Giordano M, Malaguarnera G, Bella R, Nunnari G, Rampello L, Pennisi G. *Acetyl-L-carnitine improves cognitive functions in severe hepatic encephalopathy: a randomized and controlled clinical trial*. Metab Brain Dis. 2011 Dec; 26(4): 281-9.
- 9) Malaguarnera M, Bella R, Vacante M, Giordano M, Malaguarnera G, Gargante MP, Motta M, Mistretta A, Rampello L, Pennisi G. *Acetyl-L-carnitine reduces depression and improves quality of life in patients with minimal hepatic encephalopathy*. Scand J Gastroenterol. 2011 Jun; 46(6): 750-9.

Request reprints from:

Prof. LIBORIO RAMPELLO
Direttore U.O.C. di Neurofisiopatologia
Padiglione 2 (Neurologia)
Policlinico dell'Università di Catania
V. Santa Sofia 78
95100 Catania
(Italy)