RESTLESS LEGS SYNDROME

MARCEL PEREANU[1]

[1] *"Lucian Blaga" University of Sibiu*

Keywords: *restless legs syndrome*

Abstract: *Restless legs syndrome (RLS) is a neurological sensorimotor disorder characterized by an urge or need to move the limbs, usually associated with abnormal sensations in the legs. These symptoms are aggravating at rest, are relieved by movement, and mainly occur in the evening and/or at night. RLS has a wide range of severity symptoms, varying from minimal complaints up to significant sleep disturbance and with a negative impact on the quality of life. The current understanding of the pathophysiology of RTS suggests an involvement of iron metabolism and dopamine dysfunction. Epidemiological studies indicate that the symptoms of RTS are present in about 5-10% of the general population. It results that there is a need to understand more about RLS and its way to manifest in medical practice.*

Cuvinte cheie: *sindromul de picioare neliniștite*

Rezumat: *Sindromul de picioare neliniștite (RLS) constituie o afecțiune senzitivomotorie neurologică caracterizată printr-o nevoie imperioasă de a mișca membrele inferioare, de obicei asociată cu senzații anormale la nivelul picioarelor. Aceste simptome se agravează în repaus, sunt ameliorate prin mișcare și apar cel mai frecvent seara și/sau în cursul nopții. Afecțiunea are un spectru larg de severitate care variază de la acuze foarte vagi, la afectarea somnului și a calitatii vietii, care devin suficient de severe pentru a necesita tratament medicamentos. Înțelegerea actuală a simptomatologiei RLS sugerează implicarea metabolismului fierului, precum și existența unei disfuncții dopaminergice. Studiile epidemiologice indică faptul că simptomele RLS sunt prezente la aproximativ 5-10% din populația generală. Rezultă de aici nevoia de a înțelege cât mai bine acest sindrom și modul său de manifestare în practica medicală.*

History

Restless legs syndrome (RLS) was first described by Sir Thomas Willis in 1672, but the first scientific research was conducted by Karl-Axel Ekbom, who, in his doctoral thesis in 1945, founded a modern interpretation of this condition (which is also called Willis-Ekbom disease).(1,5,7)

Epidemiology

Epidemiological studies show that RLS has a prevalence of 5-10% in the general population in the economically developed countries, only a minority (2.5%) showing daily or severe forms. Although this condition occurs quite frequently, experience suggests that it is often underdiagnosed. RLS can also occur in children, a third of them showing moderate or severe symptoms. The disease is twice more common in women than in men. About 25% of pregnant women present RLS during the third quarter of pregnancy. The most common forms of severe damage occur in middle age or old age. In a study conducted among the members of the Willis-Ekbom disease foundation, it resulted that up to 45% of patients experienced the first symptoms before the age of 20 years.(3,4,5,7)

Physiopathology

Regarding the pathophysiology of disease, the role of iron and its metabolism in the body is mentioned. On the other hand, the central dopaminergic defect is also brought forward. The connection between the two systems is the finding of low levels of iron in the substantia nigra of patients with RLS.

Moreover, it is believed that iron is an essential cofactor for the production of L-dopa, the precursor of dopamine.(2,3,5)

Etiology

The disease has two types of causes: primary and secondary.

The primary forms, idiopathic, start slowly before the age of 40-45. They are often progressive and worsen with age.

The secondary forms typically start abruptly after the age of 40. They are often progressive and can have a frequency of daily occurrence even from the beginning. They can be produced by:

- chronic diseases that cause iron deficiency (intestinal bleeding, prolonged menstruation, too frequent blood donation),
- antiemetic drugs (prochlorperazine, metoclopramide), antipsychotics (haloperidol, phenothiazines derivatives), antidepressants (which increase serotonin), antihistamines,
- pregnancy, especially in the last quarter; symptoms usually disappear after childbirth,
- other factors: alcohol abuse, sleep deprivation, etc.(11.13)

Genetics

Over 60% of cases are familial forms with autosomal dominant inheritance with variable penetrance. There were found six genetic loci responsible for the disease. Until now, there have been described four genes associated with RLS (MEIS 1 BTBD9, MAP2K5 and PTPRD).(6,9,17)

Symptomatology

RLS is manifested by the appearance of dysaesthesia,

[1]Corresponding author: Marcel Pereanu, Str. Pompeiu Onofrei, Nr. 2-4, Sibiu, România, E-mail: marcelpereanu@yahoo.com, Tel: +40269 215050
Article received on 03.07.2014 and accepted for publication on 20.08.2014
ACTA MEDICA TRANSILVANICA September 2014;2(3):213-215

unpleasant sensations that cause discomfort to the patient, manifested especially at bedtime. They are accompanied by an irresistible need to move the legs. For the improvement of complaints, the patients are often forced to get out of bed and perform a few steps across the room. The disease usually occurs spontaneously, but in some cases it may be caused by temporary immobilization of the lower limbs, such as long trips by car or bus, long-distance plane flight, watching shows or movies etc.

Symptoms vary in severity and frequency from day to day and from person to person. In severe forms, the symptoms occur more frequently than twice a week and can cause interruption of sleep and impairment of the daily activities.

The international study group on the restless legs syndrome proposed four minimum criteria for the clinical diagnosis:

- the urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensation in the legs,
- the urge to move or the unpleasant sensations begin or worsen during rest or inactivity such as lying down in bed or sitting,
- the urge to move or the unpleasant sensations are partially or totally relieved by movement such as walking or stretching at least as long as the activity is ongoing,
- the urge to move or the unpleasant sensations worsen in the evening or at night more than during day and occur only in the evening or at night.(16)

The specific criteria that define the disorder occurred in the Diagnosis and Statistical Manual of Mental Disorders 5th edition are the following:

- an urgent need to move the legs accompanied by unpleasant sensations at this level, characterized by the following: 1. the urge to move the legs begins or worsens during periods of rest of inactivity, 2. the urge to move the legs is partially or totally relieved by movement, 3. the urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.
- the above symptoms occur at least 3 times/week, and have persisted for at least 3 months.
- the above symptoms are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral or other important areas of functioning.
- the above symptoms are not attributable to another mental disorder or medical condition (such as leg cramps, arthritis, leg edema, etc.), and are not better explained by a behavioral condition (e.g., habitual foot tapping).
- the symptoms are not attributable to the physiological effects of a drug or abuse of medication.(5)

Approximately 85% of patients with RLS have periodic lower limb movements during sleep (PLMS). These are characterized by a strong and involuntary foot dorsiflexion lasting 0.5-5 seconds, occurring every 20-40 seconds during sleep.(12)

Paralcinical diagnosis

a. In RLS, the following laboratory investigations are recommended:

- iron metabolism (blood iron levels, ferritin, transferrin saturation, total iron binding capacity)
- renal tests (urea, creatinine)
- other tests (glucose, magnesium, TSH, vitamin B12, folate).

b. Electromyography (EMG) and electroneurography (ENG) for the differential diagnosis of polyneuropathy.

c. Polysomnography to quantify the periodic limb movements of sleep (PLMS) and characterize the architecture of sleep.(5)

Treatment

1**.** Pharmacological

Pharmacological treatment consists in the administration of dopamine agonists or gabapentin as first-line drugs, and opioids for resistant cases.

a. Dopaminergic agents that improve primary RLS (level A):

- levodopa is effective on short-term, in primary RLS, in order to improve sleep quality, quality of life and reducing PLMS. On long term, 30-70% have given up this medication due to side effects or ineffectiveness,
- dopamine agonists: cabergoline (0,5-2mg / day), pergolide (0.4 to 0.55 mg / day), ropinirole (1.4-4.6 mg / day) and rotigotine transdermal (the latter on short-term).(18)

b. Anticonvulsant medication

- gabapentin at a dose of 800-1800 mg / day can be considered effective in primary RLS (A level) and possibly effective in secondary RLS after hemodialysis (B level). It improves sleep efficiency and PLMS. It is indicated in moderate or severe forms,
- cabergoline (100-300 mg / day) and valproate to extended-release (600 mg / day) can be considered as probably effective in primary RLS (B level).

c. Benzodiazepines

- clonazepam (1 mg at bedtime) is probably efficient in the primary RLS and in higher doses (0,5-2mg / day) in the improvement of PLMS (B level)
- triazolam (0.125 to 0.50 mg / day) is probably effective in improving sleep.

c. Opioids

- oxycodone on an averaged dose of 11.4 mg to relieve symptoms in primary RLS, PLMS and sleep efficiency on short term (level B).

d. oral administration of iron under the form of supplement increases the ferritin levels, which in some patients may eliminate or reduce the symptoms of RLS.

2. Non-pharmacological treatment includes:

1. sleep hygiene measures,
2. avoiding caffeine, excessive alcohol consumption and smoking,
3. discontinuation of medication that exacerbate RLS, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), dopamine antagonists,
4. physical exercises before going to bed.(8,14,15,16,17)

REFERENCES

1. Allen RP, Earley CJ. Restless Legs Syndrome. Journal of Clinical Neurophysiology 2001;18:128-47.
2. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Medicine 2004;5:385-91.
3. Allen R, Picchietti D, Hening WA et al. Restless Legs Syndrome Diagnosis Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Medicine 2003;4:101-19.
4. Allen RP, Walters AS, Montplaisir J et al. Restless legs

syndrome and impact. Arch Intern Med 2005;5:1286-1292.
5. Bozorg AM. Restless Legs Syndrome. 2014. WWW Medscape.
6. Connor J.R., Boyer P.J, Menzies S.L, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304-9.
7. Earley CJ. Restless Legs Syndrome. New England Journal of Medicine 2003;348:2103-9.
8. Earley J, Silber MH. Restless legs syndrome: Understanding its consequences and the need for better treatment. Sleep Medicine 2010;11:807-15.
9. Earley C, Barker P, Horská A, Allen R. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Medicine 2006;7:458-61.
10. Garcia-Borreguero D, Stillman P, Benes H, et all. Algorithms for the diagnosis and treatment of Willis-Ekbom Diseae/restless legs syndrome in primary care. BMC Neurology 2011;11:28.
11. Hening W, Walters AS, Allen RP et al. Impact diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep medicine 2004;5:237-246.
12. Karatas M. Restless Legs Syndrome and Periodic Limb Movements During Sleep: Diagnosis and Treatment. The Neurologist 2007;13 294-301.
13. Pantaleo NP, Hening WA, Allen RP, Earley CJ. Pregnancy accounts for most of the gender difference in prevalence of familial RLS. Sleep Medicine 2010;11:310-313.
14. Rottach K, Schaner B, Kirch M et al. Restless legs syndrome as side effect of second generation antidepressants. Journal of Psychiatric Research 2008;43:70-5.
15. Silber MH, Ehrenberg BL, Allen RP et al. Medical Advisory Board of the Restless Legs Syndrome Foundation (2004). An Algorithm for the Management of Restless Legs Syndrome. Mayo Clinic Proceedings 2004;79:916-22.
16. Vignatelli L, Billiard M, Clarenbach P et al. Recomandarile EFNS privind sindromul picioarelor nelinistite si sindromul miscarii periodice a membrelor in somn. In: Bajenaru O. (coordonator stiintific) Ghiduri de diagnostic si tratament in neurologie. Edit. Amaltea. Bucuresti; 2012. p. 507-516.
17. Xiong L., Montplaisir J, Desautels A et.al. Family Study of Restless Legs Syndrome in Quebec, Canada: Clinical Characterization of 671 Familial Cases. Archives of Neurology 2010;67:617-22.
18. Zintzaras E, Kitsios GD, Papathanasiou AA et al. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. Clinical therapeutics 2010;32:221-37.