CLINICAL ASPECTS

RESTLESS LEGS SYNDROME

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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 RLS suggests an involvement of iron metabolism and dopamine dysfunction. Epidemiological studies indicate that the symptoms of RLS are present in about 3-10% of the general population. It results that there is a need to understand more about RLS and its way to manifest in medical practice.

Keywords: restless legs syndrome
Cuvinte cheie: sindromul de picioare neliniștite

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),
  - 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,
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 or 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)

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