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Etiopathogenetic Aspects of Secondary Restless Legs Syndrome

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Abstract: Restless legs syndrome (RLS) is a sensorimotor disorder characterized by unpleasant sensations in the lower extremities that appear at rest (more often in the evening and at night), force the patient to make movements that facilitate them and often lead to sleep disturbance.

Keywords: restless legs syndrome, somatic disease, autosomal dominant type, external factors

More than half of the cases of RLS occur in the absence of any other neurological or somatic disease (primary or idiopathic RLS). RLS was first described by Thomas Willis in 1672, but the systematic study of the syndrome began only in the 1940s with the work of the Swedish neurologist K.A. Ekbom, after whom RLS was named Ekbom's syndrome [7]. Primary RLS usually appears in the first three decades of life (early-onset RLS) and may be hereditary. In various clinical series of RLS, the proportion of familial cases ranged from 30 to 92%. Analysis of family cases indicates a possible autosomal dominant type of transmission with almost complete penetrance, but variable expressivity of the pathological gene. Assume both polygenic and monogenic nature of the disease. In some families, RLS was found to be associated with loci on chromosomes 12, 14, and 9. Perhaps, in a significant part of cases, the disease has a multifactorial nature, arising as a result of a complex interaction of genetic and external factors [3, 5, 8].

Symptomatic (secondary) RLS often debuts after 45 years (late-onset RLS) [2, 5]. The three main causes of secondary RLS are pregnancy, uremia, and iron deficiency (with or without anemia). RLS is detected in 15-80% of patients with uremia (most often in dialysis patients) and in almost 20% of pregnant women. In pregnant women, symptoms appear only in the II-III trimester and disappear within a month after delivery, but sometimes persist persistently. In addition, cases of RLS are described in diabetes mellitus, amyloidosis, cryoglobulinemia, deficiency of vitamin B12, folic acid, thiamine, magnesium, alcoholism, thyroid diseases, rheumatoid arthritis, Sjögren's syndrome, porphyria, obliterating diseases. arteries or chronic venous insufficiency of the lower extremities.

RLS has also been described in patients with radiculopathies, as well as lesions of the spinal cord, usually in the cervical or thoracic regions (for example, with injuries, spondylogenic cervical myelopathy, tumors, myelitis, multiple sclerosis).

It is possible that in some patients with RLS, iron deficiency, coffee abuse, polyneuropathy, or other factors only reveal an existing hereditary predisposition, which partly blurs the boundary between primary and secondary variants of RLS [2].

General and neurological examinations in patients with primary RLS usually do not reveal any abnormalities. But with symptomatic RLS, signs of a somatic or neurological disease, primarily

polyneuropathy, can be detected.

In primary RLS, symptoms usually persist throughout life, but their intensity can fluctuate significantly - it temporarily increases during periods of stress, due to the use of caffeine-containing foods, after intense physical exertion, during pregnancy. In most cases, over time, there is a tendency to a slow increase in symptoms. But sometimes there are periods of stationary flow or remission, which can last from several days to several years. Long-term remissions are observed in 15% of patients. In secondary RLS, the course depends on the underlying disease, but there is often a tendency to a rapid increase in symptoms. Spontaneous remissions in symptomatic forms are rare [3, 4, 5].

Modern population studies show that the prevalence of RLS among the adult population is 5-10% [5, 15]. RLS occurs in all age groups, but is more common in middle and old age (in this age group, its prevalence reaches 10-15%) [21]. According to a number of researchers, about 15% of cases of chronic insomnia are associated with RLS [8].

Thus, RLS should be attributed to frequent diseases, but is rarely diagnosed, mainly due to the low awareness of practitioners, who often tend to explain the complaints of patients with neurosis, psychological stress, diseases of peripheral vessels, joints or spine . Nevertheless, in most cases, the diagnosis of RLS is not difficult and is based mainly on the clinical analysis of the patient's complaints.

Syndromic diagnosis of restless leg syndrome

Clinically, RLS is characterized by two main groups of symptoms: subjective pathological sensations and excessive motor activity, which are closely related.

Sensory symptoms of RLS are represented by sensations of itching, scraping, stabbing, bursting or pressing, a feeling of crawling. Some patients complain of dull, aching or intense cutting pain, but more often these sensations are not painful, although they can be extremely painful and unpleasant. Painful pathological sensations experienced by patients are usually referred to as dysesthesias, non-painful ones - as paresthesias, however, the boundary between them is conditional [4].

Pathological sensations in RLS initially have a limited localization and occur in the depths of the legs, much less often (usually with polyneuropathy) - in the feet. With subsequent progression, they often spread upward, involving the hips and arms, and occasionally the trunk and perineum. Unpleasant sensations usually occur on both sides, but in more than 40% of cases they are asymmetrical, and sometimes even one-sided.

A characteristic feature of pathological sensations in RLS is depending on motor activity and posture. Usually they arise and increase at rest (in a sitting position and especially lying down), but decrease with movement. To alleviate their condition, patients are forced to stretch and bend their limbs, shake, rub and massage them, toss and turn in bed, get up and walk around the room or shift from foot to foot. During movement, unpleasant sensations decrease or disappear, but as soon as the patient lies down, and sometimes just stops, they increase again. Each patient eventually forms his own repertoire of movements that help him reduce discomfort in the limbs. RLS symptoms have a clear daily rhythm, appearing or intensifying in the evening and at night. On average, symptoms reach their maximum severity between 0000 and 4000 hours in the morning, and their minimum severity between 0600 and 1000 hours in the morning. Initially, most patients develop symptoms about 15 to 30 minutes after they go to bed. But in the subsequent time of their appearance may become ever earlier, up to daylight hours. In severe cases, the characteristic circadian rhythm disappears and the symptoms become permanent. They can occur not only in the supine position, but also in the sitting position and can make it unbearable to visit the cinema or theater, flying on an airplane, a long trip in a car.

A direct consequence of unpleasant sensations in the limbs and the need to constantly make movements is sleep disturbance - insomnia. The complaint of poor sleep is the leading complaint in most patients, and it is she who most often leads them to the doctor. The consequence of insomnia is rapid fatigue and reduced attention during the daytime. Many patients have comorbid depression.

Sleep disturbances in RLS exacerbate periodic limb movements (PLM), which occur during sleep in 80% of patients with RLS. They are rhythmic short-term twitches, which are most often observed in the legs, are stereotypical in nature and include dorsiflexion of the big toes, sometimes with a fan-shaped separation of the remaining fingers or flexion of the entire foot. In more severe cases, flexion of the legs at the knee and hip joints also occurs. MPC lasts from 0.5 to 5 s and occurs in series at intervals of 20-40 seconds for several minutes or hours. In mild cases, neither the patients themselves nor their close relatives are aware of the presence of MPC, and they can only be detected using polysomnography. In severe cases, the movements do not stop all night and may cause frequent awakenings. In general, the intensity of MPC correlates well with the severity of RLS manifestations, so their registration using polysomnography can serve as a reliable objective method for assessing the effectiveness of RLS therapy [11].

Table 1. Criteria for diagnosing restless leg syndrome [4]

Feature categories	Description of features
Mandatory Criteria	The urge (urge) to move the legs, usually associated with or caused by discomfort in the legs (the urge to move may not be accompanied by discomfort, the arms and other parts of the body may be involved). The urge to move or discomfort begins or worsens during rest or inactivity. The urge to move or the discomfort is partially or wholly relieved by the movement for as long as it lasts. Urges to move or discomfort are more pronounced in the evening and at night than during the day. In the most severe cases, nocturnal aggravation may not be noticeable but should be noted earlier.
Confirming clinical signs	Positive family history Response to dopaminergic drugs (> 90%) Periodic leg movements (during wakefulness or sleep)
Associated clinical signs	Natural clinical course* Sleep disorders No changes on physical and neurological examination**

Note. * - chronic stationary or slowly progressive course with periods of deterioration and improvement or remission; ** - in the primary form.

The RLS diagnostic criteria proposed by the International RLS Research Group [4] are presented in Table 1.

RLS has to be differentiated from akathisia, painful feet-moving toes syndrome, hypnic twitches, nocturnal cramps, paresthetic meralgia, sensory manifestations of polyneuropathy, and fibromyalgia. With a deviation from the typical clinical picture of the syndrome or with the ineffectiveness of standard therapy, polysomnography is indicated to confirm the diagnosis.

Nosological diagnosis of restless leg syndrome

After diagnosing RLS, it is necessary, first of all, to exclude its secondary nature by conducting a thorough neurological and somatic examination of the patient. The volume of laboratory and instrumental examinations is dictated by the need to exclude polyneuropathy (including with the help of stimulation and needle electroneuromyography), diseases of the spinal cord, peripheral vessels, iron deficiency, anemia, uremia, liver failure, diabetes mellitus, chronic lung diseases, rheumatic diseases, deficiency of magnesium and vitamins. It should be emphasized that the level of ferritin,

rather than serum iron, more reliably indicates iron deficiency in the body.

Treatment of the underlying disease

With symptomatic RLS, treatment should first of all be aimed at correcting the primary disease or replenishing the identified deficiency (iron, folic acid, magnesium, etc.). Correction of iron deficiency with the appointment of iron preparations is indicated in the case when the serum ferritin content is below 50 μg / ml. Usually appoint ferrous sulfate, gluconate or fumarate at a dose of 325 mg (65 mg of elemental iron) in combination with vitamin C (100-200 mg) 2-3 times a day between meals. A faster effect is given by intravenous administration of iron dextran (100-200 mg of elemental iron every 1-4 days). Treatment is carried out under the control of ferritin, the level of which should be maintained at a level above 50 mcg / l. Iron overload, which threatens the development of hemochromatosis, should be avoided.

You should also cancel the means that can increase the manifestations of RLS:

- ✓ neuroleptics and other antidopaminergic agents (metoclopramide);
- ✓ antidepressants: tricyclic, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, mirtazapine;
- ✓ lithium preparations;
- ✓ adrenomimetics (terbutaline);
- ✓ antihistamines (with the exception of drugs that do not cross the blood-brain barrier, such as loratadine);
- ✓ H2 receptor antagonists;
- ✓ nifedipine and other calcium antagonists;
- ✓ beta-blockers.

In primary RLS, symptomatic therapy is the mainstay of treatment, with the help of which it is possible to achieve complete regression of symptoms in a significant proportion of patients.

Non-pharmacological treatment of restless leg syndrome

All patients are recommended moderate physical activity during the day, compliance with a certain ritual of going to bed, evening walks, evening showers, a balanced diet with the refusal to drink coffee, strong tea and other caffeine-containing products (for example, chocolate or Coca-Cola), alcohol restriction, smoking cessation, normalization of the daily routine.

More K.A. Eckhom (1945) noted that the symptoms of RLS are more pronounced in patients with cold feet, while they decrease with an increase in body temperature. In this regard, a warm foot bath or a light warming foot massage before going to bed can significantly improve the condition. In some cases, transcutaneous electrical stimulation, vibromassage, darsonvalization of the legs, reflexotherapy or magnetotherapy are effective.

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