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PATHOPHYSIOLOGY AND CLINICAL FEATURES OF RESTLESS LEGS SYNDROME

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ABSTRACT

Restless legs syndrome is a chronic sensorimotor disorder that involves sensory discomfort in the legs or other parts of the body, arising or increasing at rest, in the evening / night, and causing the need for movement. Despite the high prevalence and a significant impact on the quality of life, general practitioners, first-level specialists and the neurologists themselves are not sufficiently aware of this disease, and therefore it often remains a misdiagnosed state.

KEYWORDS: restless legs syndrome, periodic limb movement.

INTRODUCTION

Restless legs syndrome (RLS) also known as Willis-Ekbom disease is a sensorimotor disorder characterized by unpleasant sensations in the lower limbs, which appear at rest (often in the evening and at night), make the patient to make movements that facilitate them and often lead to sleep disturbance.[1,2]

According to numerous studies, the prevalence of RLS in the population of Western Europe and North America ranges from 2.5-3 to 15%, an average of 5-10%.[6,7] In Asian countries, the prevalence of RLS is lower and ranges from 0.1 to 1.5%.[11,12] RLS can develop in any age group, but as its age increases, its prevalence increases. In the population of the United States and the United Kingdom, the prevalence of RLS is 1.9% in children (under 14 years of age), 2% among adolescents (over 14 years of age).[5,14] The prevalence of RLS clearly increases with the age of 20, reaching a peak of 70–79 years and then decreases.[15] Women suffer an average of 2 times more often.[13] The severity of symptoms varies from isolated episodes to an extremely severe degree with a complete loss of sleep. Clinically significant RLS is beginning with a moderate degree of severity, as determined by the international scale of assessing the severity of RLS - International RLS Severity Scale, IRLSSS. The prevalence of such forms of the disease, in which the symptoms occur at least 2 times a week and determine the need to seek medical help, is 1-3% in the population or about 15% of all cases of RLS.[11,15,17]

Etiopathogenesis. Despite the active study and use of modern instrumental methods, the pathophysiology of RLS remains poorly understood. Involve the involvement of many structures and systems of the brain and spinal cord and the associated peripheral sensorimotor apparatus.

The leading molecular mechanisms in RLS are:
1) Pathology of the dopaminergic system, which involves the opioid, noradrenergic systems, GABA and NMDA receptors at several levels in the pathogenesis;
2) Specific disorders in iron metabolism in the central nervous system (CNS).[18]

These hypotheses are confirmed by the high efficacy of dopaminergic, opioid drugs, as well as anticonvulsants and iron preparations in the treatment of RLS.

The key role in the pathogenesis of RLS is played by the segmental apparatus of spinal cord and one of the main regulators of its activity is the dopamine system.

At this level, it is assumed that one or both mechanisms are involved — spinal cord anxiety or reduced activating effect of the descending cortical pathways.[19] The source of these changes in excitability may be the pathology of the descending modulating pathways, such as spinal dopaminergic, associated, in turn, with the dopamine-containing group of cells of the A11 zone located near the suprachiasmatic nucleus - one of the main regulators of circadian rhythms.[20] Among the brain structures, candidates for participation in the pathogenesis of RLS are the thalamus, large cells of the red nucleus, the lower olive and the cerebellum.[18] Thus, two independent groups of researchers in Regensburg and Munich, using high-field T1-weighted magnetic resonance imaging (MRI) using voxel morphometry, demonstrated

significant morphological changes in thalamic structures, including putamen, in patients with RLS.[21]

The involvement of the basal ganglia in the pathogenesis of RLS is not proven and is denied by most researchers.[18,22] Convincing evidence of direct involvement of the cerebral cortex in the pathogenesis of RLS is not obtained. In particular, transcranial magnetic stimulation did not reveal the pathology of the corticospinal tract in patients with RLS and MPC.[19] The study of dopamine metabolism in the brain revealed that iron is an important participant in this process.[23] Disturbance of its metabolism can play a key role in the pathogenesis of RLS, arising due to changes at several levels: impaired iron uptake by neuromelanin cells, impaired regulation of transferrin receptors of the blood-brain barrier endothelial cells, pathology of iron regulating proteins and bivalent carriers of metal ions in the microvascular bed of the brain.[24,25] Thyroid hormones are also involved in dopamine metabolism. The latter made it possible to propose a hypothesis about the pathogenetic relationship between the violation of the status of thyroid hormones and the occurrence of RLS.[26] It should be noted that the exchange of dopamine has a specific diurnal rhythm, which coincides with the characteristic fluctuation of symptoms characteristic of RLS.[18,27]

Sensomotor disorders in RLS, as well as the frequent association of RLS with neuropathy, suggested a relationship between these pathologies. Thus, it was found that the balance between the descending inhibitory and excitatory pathways involved in the pathogenesis of RLS at the segmental level of the spinal cord is disturbed after nerve damage.[18] Special attention was paid to the neuropathy of fine fibers - A-delta and C-fibers. Several studies have confirmed the neurophysiological and morphometric correlates of damage to small-diameter fibers in RLS, including in the patient group, which was previously regarded as idiopathic.[18,19] An increase in the threshold of temperature sensitivity (for cold and warm), as well as signs of axonal degeneration and death of sural nerve fibers (according to biopsy data) were repeatedly found. However, an unambiguous pathogenetic relationship between RLS and neuropathy, including fine fibers, was not found.[19,28]

Clinical Picture: Primary (Idiopathic) Form of Rls.

In 40–60% of primary forms of RLS, a family history is found. This form is characterized by an earlier debut of symptoms: 35.4 years compared with 47.1 years for the secondary form.[19] The progression of the disease varies: it is possible as an early debut, up to 30 years, - 50% of cases,[9] with a slow increase in symptoms for many years and no daily symptoms until the age of 40–60 years,[15] and late manifestation, with which has a faster progression. The variant of the course of the disease is difficult to predict. Spontaneous remission is possible. When considering the genetic factors of primary RLS, if the patient has the first symptoms before the age of 45, the first-line relatives have a higher risk of developing RLS than in the manifestation after 45 years or in the control group (23.6; 10 and 3.5%, respectively).[7] Early debut forms are genetically different from forms with a later manifestation (after 30 years), are characterized by an autosomal dominant mode of inheritance, and are due to a mutation in one specific gene.[31] The genetic risk for the development of the idiopathic form of RLS is associated with the MEIS1, BTBD9 and MAP2KP/LBXCOR loci of chromosomes 2p, 6p and 15q, respectively.[32] The BTBD9 locus has the greatest influence.[19] whose representation in the population of northern Europe is higher than, for example, in the Far East (65% of healthy representatives). This locus is also associated with MPC, Tourette syndrome, hyperactivity syndrome and attention deficit.

Symptomatic form of RLS occurs on the background of the main pathology, on which, among other things, depends on the age of the onset of RLS symptoms. Secondary RLS is characterized by a remitting course and a regression against the background of the correction of the main pathology.[11] In most cases, sensory discomfort occurs in the legs (mainly in the legs), but it can also be present in the hands, torso and face.[13,14] Patients with RLS specifically describe sensitive symptoms.[9] In addition to paresthesias, dysesthesies and other similar descriptions, complaints may acquire a senesthopathic hue, and up to 50% of cases they have a painful nature.[5]

Examples of the description of sensory discomfort in the legs with RLS.[9] are the following characteristics: “calves are lowered into boiling water”, “crawling”, “jerking, tension in the legs”, “burning in the legs”, “painful warmth in the legs”, “insects crawling in the calf”, “blood boils in the legs”, “painful, undifferentiated painful sensations”, “trembling in the muscles”, “twisting the legs”. There are some cases when sensory sensations are absent. In such a situation, involuntary spasmodic twitching (or “jerky” from the English jerks - flinching, jerking) can be observed - the so-called motor variant of the sc. Twitching data, also called dyskinesia during wakefulness, can affect 1 limb or the whole body, also appear at rest and disappear when moving.[29] The need for movement or discomfort arises or is aggravated at rest. The need for movement of the limbs or discomfort in them arises or is aggravated at rest, sitting or lying. The absence of movement and the decrease in the activating influence of the central nervous system play a triggering role in this.[23]

The need for movement or discomfort partially or completely regress as a result of motor activity, or at least during the entire time it is maintained. Regression of sensory sensations in RLS occurs against the background of the activation of the motor system, which is due to the pathogenesis of the disease.[18] Movement can be performed with 1 or 2 limbs at once, and its intensity depends on the stage of the disease. Therefore,

in advanced stages of the disease, limb movement may not bring relief. Sometimes massage or any tactile stimulation of the limbs, in which sensory discomfort occurs, as well as water procedures (footbaths, showers with alternating warm and cool water) can cause a regression of symptoms [12]. The need for movement or discomfort is exacerbated in the evening / night or occurs exclusively in the evening or at night. This phenomenon is due to the connection of the manifestations of the disease with a circadian rhythm and is obligatory in the opening for diagnosis. Symptoms increase 1–2 hours after midnight, and then decline.[27] This rhythm coincides with a decrease in the daily bioavailability of iron, which, in turn, may inhibit the synthesis of dopamine.[23] Symptomatology can occur in the daytime, as a rule, it is observed in advanced stages. In one study, the symptoms of RLS were detected in the daytime in more than 40% of cases.[16]

Often, sensorimotor disorders typical for RLS are not dominant in the clinical picture and, accordingly, are not well reflected in the patient's complaints, and secondary or associated with RLS disorders come to the fore.[26] According to research data, more than 75% of RLS patients present at least 1 complaint of sleep disorders.[16,23] The latter include difficulties with primary and repeated sleep, intermittent sleep due to motor phenomena in the limbs.[25] Sleep disorders in RLS due to its circadian rhythm (in the evening and early-night hours, up to 2-4 hours, symptoms of RLS reach a peak), as well as the concomitant syndrome of periodic limb movements during sleep. Despite a lack of sleep, excess daytime sleepiness is rare in RLS. The test of multiple latency to sleep (MSLT, multiple sleep latency test) revealed a moderately pronounced excessive daytime sleepiness or lack thereof.[21]

Anxiety-depressive disorders often occur with RLS, being dominant in the patient's complaints. They can also be associated with a decrease in everyday and social activity during the daytime and sometimes cognitive disorders.[10,31]

DIAGNOSTIC METHODS

According to an international REST study conducted in the United States and 5 European countries, out of 64.8% of patients presenting complaints typical for RLS, only 12.9% were diagnosed with RLS. At the same time, according to the general practitioner, only 37.9% of patients presented complaints characteristic of RLS, and only 24.9% were diagnosed with RLS.[16] Similar results were obtained in large-scale studies conducted in the US, UK and Ireland.

Despite the high prevalence and significance of the effects of RLS on the quality of life,[10] the disease often remains misdiagnosed. Difficulties in diagnosis are associated both with low awareness of doctors (general practitioners and neurologists), and with the unusual and to a certain extent insufficiently specific nature of complaints encountered in other diseases, as well as the fact that in a large percentage of cases the leading clinical signs are non-sensomotor disturbances, and secondary manifestations. Thus, according to a population-based study conducted in Germany, the ratio of diagnosed RLS to non-diagnosable was 1: 3.[29] In the French study, the percentage of patients with RLS who were diagnosed with this diagnosis was only 5.3, whereas 53% of the sample presented complaints typical of this disease, and 60% of patients had previously been diagnosed with foot vascular disease, mainly venous.[29]

Practicing doctors often tend to explain complaints of patients with neurosis, psychological stress, diseases of peripheral vessels, joints, spinal osteochondrosis. However, in most cases, the diagnosis of RLS is simple and is based on the complaints of the patient.

The diagnosis of RLS is exclusively clinical. Therefore, its formulation requires compliance with 4 clinical characteristics. Additional criteria, concomitant symptoms, laboratory and instrumental methods used to confirm them are not necessary; however, they are a good help in cases of fuzzy symptoms, and also help to determine the type of RLS.

The last modification of the diagnostic algorithm for RLS for the adult population, compiled in 2002 during the NIH round table,[9] is as follows.

Main criteria

1. The need to move the legs or other parts of the body, arising, as a rule, against the background of unpleasant sensations in them.
2. The need for movement or discomfort arises or is aggravated at rest.
3. The need for movement or unpleasant sensations partially or completely regress because of motor activity or at least during the whole time of its maintenance.
4. The need for movement or discomfort is aggravated or occurs exclusively in the evening / night.

Supporting criteria

1. Family history of RLS.
2. The positive effect of dopaminergic drugs.
3. The presence of periodic limb movements (MPC) during sleep (MPC) or wakefulness (MPC), identified by polysomnography or other studies.

Related criteria

1. Progressive course of the disease.
2. Sleep disorders.
3. Absence of pathology in the neurological status in the primary form of RLS.
4. Elimination of possible causes of secondary sconitis.

Separate criteria for the diagnosis of RLS were developed for children 2–12 years old, including 4 main criteria for RLS established for adults, as well as

supporting criteria taking into account the nature of the description of complaints in childhood and the possible difference in the manifestation of the disease in comparison with the adult form

Having diagnosed RLS, the secondary nature of the syndrome should be excluded after a thorough neurological and somatic examination of the patient. The scope of laboratory and instrumental examination is dictated by the need to exclude polyneuropathy (including using electroneuromyography), anemia, uremia, diabetes mellitus, chronic lung diseases, rheumatic diseases, iron deficiency, magnesium and vitamins. It should be noted that the level of ferritin, rather than serum iron, more reliably indicates an iron deficiency in the body. If there is a deviation from the typical clinical picture of the syndrome or if the standard therapy fails, polysomnography is shown.

Differential diagnosis: RLS has to be differentiated with akathisia, the syndrome of "painful legs - moving fingers", hypnical jerking, night cramps, paraesthetic meralgia, polyneuropathy, fibromyalgia.

Treatment

Difficulties are associated not only with the diagnosis, but also with the appointment of adequate treatment. Thus, according to DESYR, the most frequent drugs prescribed for RLS are just those drugs that can exacerbate symptoms.[48] In case of secondary RLS, the main somatic or neurological disease is treated. If the content of ferritin in the blood plasma is less than 50μg/L, iron preparations are prescribed in combination with vitamin C 3 times a day.

For primary and secondary RLS, it is recommended to quit smoking, drinking caffeinated beverages, and alcohol. Recommended sleep hygiene (sleep at a certain time, evening walks, warm showers), foot massage, very hot or very cold foot baths, moderate exercise, normalization of the day regimen. Physical therapy, reflexology have a certain positive effect only in some cases. The decision on the need for the appointment of drug therapy should take into account several factors: the severity of symptoms, the presence of pain, sleep disorders, impaired quality of life and the daily activity of the patient.

Common therapeutic approaches to the treatment of RLS are

Cancellation of medications that may worsen the course of RLS (dopamine receptor antagonists, antidepressants, lithium preparations, antihistamines, calcium antagonists, (β-blockers).

Treatment of the underlying somatic and neurological disease in secondary RLS.

Accounting for the patient's age and the degree of risk of side effects of pharmacotherapy.

Consideration of the severity of RLS and its influence on sleep and the patient's quality of life.

Determination of the dose, frequency and time of medication.

Start therapy with minimal therapeutic doses.

Slow titration of the dose with a gradual increase to the minimum effective.
Evaluation of the validity of combination therapy with the ineffectiveness of monoterania.

Pharmacotherapy for RLS is prescribed for a progressive course of the disease, severe insomnia, daytime sleepiness and a significant deterioration in the daily activities and quality of life of patients; on average, only 20-25% of patients need it. The main drugs prescribed for RLS are dopaminergic drugs, anticonvulsants, benzodiazepines, onioids.

Dopaminergic drugs (dopamine receptor agonists, levodopa) are the most widely studied in RLS and are the first choice drugs for the treatment of both primary and secondary syndromes.

Levodopa in patients with acute malignant neoplasia has been used since 1987. Levodopa is prescribed in combination with a DOPA-decarboxylase inhibitor DDC (benserazide or carbidopa) at a dose of 50 mg 1 hour before sleep, and subsequently with insufficient efficiency, the dose is increased to 100-200 mg However, two important complications of prolonged levodopa therapy can be observed in the treatment of RLS - augmentation (intensification of symptoms) and the rebound phenomenon. The recoil phenomenon occurs in 46% of cases already after 6 months of continuous intake of 160 mg of levodopa. It is manifested by the return of symptoms in the second half of the night or in the early morning after an evening dose of levodopa. The recoil phenomenon can be reduced by prescribing prolonged forms of levodopa preparations with a sustained release of the active substance or by taking an additional dose of levodopa when symptoms return. Augmentation is manifested by an increase in the severity of RLS and an earlier onset of symptoms during treatment. This phenomenon develops in 80% of cases after 2 months use of levodopa for RLS.

With the development of augmentation is necessary

- Check plasma ferritin levels and, if necessary, prescribe iron supplements
- Reduce the dose of levodopa or resort to crushing it
- Prescribe levodopa supplementation at an earlier time
- Add dopamine receptor agonists (ADAR) or completely switch from levodopa to ADAR

- Replace dopaminergic drugs with anticonvulsants, benzodiazepines.

Augmentation occurs much less frequently when ADAR is prescribed - no more often than in 20-30% of cases.

With insufficient efficacy of dopaminergic agents, anticonvulsants and benzodiazepines are prescribed. Opioids are usually used only for severe RLS in patients with severe pain, with daytime symptoms; as well as in the case of the ineffectiveness of other medicines.

CONCLUSION

Treatment of RLS is sometimes carried out only during the period of amplification of symptoms, but in most cases, primary RLS therapy is carried out for a long time, sometimes throughout life. Dopaminergic therapy is most effective for RLS and can be used as an additional diagnostic criterion for this disease. Drugs of the first choice of therapy for SOS are ADAR.

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