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CURRENT VIEWS ON THE DIAGNOSIS AND TREATMENT OF RESTLESS LEGS SYNDROME

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Abstract: Restless legs syndrome is a neurological disorder in which unpleasant sensations in the legs (less often in the arms) cause an irresistible need to move the limbs. Burning, tingling and goosebumps occur at rest, especially when lying down, in the evening and at night. These symptoms diminish or disappear completely when moving.

Key words: restless legs syndrome, neurology, varicose veins of the legs.

Introduction. The disorder is manifested by a range of symptoms. Patients experience unpleasant sensations in the legs such as burning, tingling, numbness, “twisting”. They may complain of tumescence or a feeling of pressure, “goosebumps” or other distressing anxiety. A number of patients talk about constant discomfort in the legs of the type of pain of a nagging nature, unpleasant more by its severity than painfulness.

Unpleasant sensations arise in the lower legs, often spreading higher: in the thighs, and sometimes even in the trunk, perineum and arms. Symptoms are usually symmetrical, although there have been cases of asymmetrical or unilateral sensations.

Usually the syndrome makes itself known in the evening and at night, when a person rests lying or sitting. The resulting unpleasant sensations are reduced by movement, so patients in order to reduce the symptoms perform a variety of actions: turning in bed, get up and walk around the room, bending and extending legs, give themselves a massage, rubbing limbs, squatting, etc. When the movements cease, the symptoms gradually return. The appearance of signs of restless legs syndrome, as a rule, has a circadian character, ie depends on the time of day. They are most pronounced from midnight to 2-4 am [3]. In the case of a severe form of this disorder, symptoms may occur around the clock [8]. Therefore, patients also have sleep disorders, in particular insomnia (insomnia). It is characterized by difficulty falling asleep, anxiety and fewer hours of sleep, which is the cause of daytime sleepiness and fatigue during the day. Insomnia significantly reduces performance, contributes to the development of depression and anxiety disorder [6].

The vast majority of patients with restless legs syndrome have periodic involuntary rhythmic short-term rhythmic leg twitches [15]. As a rule, they occur in the first and second phase of slow-wave sleep, so the patients themselves and their loved ones may not notice such movements. Usually, this symptom is detected during polysomnography, a special study that is performed in laboratories that study sleep.

The most significant evidence for the theory of dopaminergic system deficiency as the cause of primary restless legs syndrome is the high efficacy of dopamine and its agonists in treating the disorder.

Classification and stages of development of restless legs syndrome

Depending on the clinical picture of the disorder, there are three degrees of severity of the syndrome:

- Mild degree - unpleasant sensations in the legs bother episodically, significant sleep disturbances are not observed, the quality of life of the patient practically does not suffer;
- moderate degree - unpleasant sensations in the legs bother less than twice a week, sleep and quality of life are moderately disturbed as a result;
- Severe degree - unpleasant sensations in the legs bother twice a week and more often, sleep and quality of life are severely disturbed.

According to its duration, the syndrome can be acute, subacute and chronic. In the acute form of the disorder, the symptoms bother the patient for no more than two weeks, in the subacute form - for no more than three months, in the chronic form - for longer than three months [13]. However, in general, the course of the disease is chronic. The periods of remission of the syndrome can last either a few days or several years [12].

The primary syndrome, which occurs independently of other conditions and diseases, usually develops in 30-40 years of age, has long periods of stable course without an increase in symptomatology. If the disorder occurs in later old age and senility, the course of the disorder may be more severe and resistant to treatment.

Complications of restless legs syndrome

As complications of the syndrome can be considered insomnia (insomnia) and the changes caused by it: anxiety, stress and other mental and behavioral disorders. Due to the fact that the patient has to wake up constantly at night, during the day he becomes sleepy, irritable, emotionally unstable. Due to the lack of energy, he quickly becomes fatigued, his physical and mental performance decreases, there are problems with concentration. All this worsens the quality of life and affects the health of the patient. In particular, women diagnosed with restless legs syndrome have an increased risk of developing clinical depression [9]. As a rule, depression regresses after the disappearance of the syndrome signs [14].

Diagnosis of restless legs syndrome

Diagnosis of the syndrome, as a rule, does not cause difficulties. It is carried out on the basis of the patient's complaints. The initial examination usually does not reveal any abnormalities.

When making a diagnosis, doctors are guided by the diagnostic criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG) [10]. According to these criteria, updated in 2012, a patient with this syndrome must have all five features of the disorder:

1. Forced leg movements are usually accompanied or triggered by discomfort and discomfort in the legs.
2. The leg discomfort and associated desire to move the limbs occur or increase during periods of rest or inactivity in the supine or sitting position.
3. The need to move the legs and the unpleasant sensations are completely or partially eliminated by movements such as walking or stretching (at least for the duration of the movement).
4. Leg discomfort and urges to move appear or worsen in the evening or at night, but not throughout the day.
5. The symptoms listed above are not a manifestation of another medical or behavioral condition.

Given the latter criterion, it is important to distinguish restless legs syndrome from other pathologies in the diagnostic search:

- peripheral polyneuropathy;
- vascular diseases (varicose veins, atherosclerosis of the arteries of the lower extremities, endarteritis, deep vein thrombosis);

- swelling of the lower extremities;
- myalgia (muscle pain);
- arthritis and other joint diseases;
- anxiety disorder;
- positional discomfort;
- thyroid disorders;
- crimpy - sudden painful involuntary contractions of the leg muscles lasting from a few seconds to several minutes;
- akathisia - pathological “inattentiveness” due to discomfort not related to the position of the body or time of day (often the result of taking neuroleptics).

To make a diagnosis, it is also necessary to examine the iron stores in the body, assess the function of the kidneys, thyroid gland, and carbohydrate metabolism. For these purposes, a general blood test is performed. The levels of ferritin, transferrin, total serum iron-binding capacity, folic acid, vitamin B12, glucose, glycated hemoglobin, creatinine, urea, uric acid, albumin, thyroid hormone, and free thyroxine can also be determined [3].

In some cases, the doctor may prescribe polysomnography - a sleep study using specialized sensors and programs. With its help, an expanded picture of the patient's sleep parameters, data on the patient's motor activity, including the number of periodic limb movements, are obtained.

Pathogenesis of restless legs syndrome

According to studies, patients with restless legs syndrome have a reduced supply of iron in the brain and cerebrospinal fluid [7,8]. The deficiency of this element leads to a lack of dopamine and myelin, as well as a decrease in energy synthesis in neurons. Among specialists studying this problem, the prevailing opinion is that these changes in restless legs syndrome are based on a disruption of dopamine transmission in the central nervous system. However, to date, there is no unified explanation of the processes that lead to the development of primary restless legs syndrome. The clear dependence of the symptoms of the disorder on the diurnal cycle is explained by the fact that it is in the evening that patients have the lowest levels of dopamine and its metabolites in the cerebrospinal fluid and intercellular space [8,12]. In addition, the distinct circadian rhythm of the syndrome manifestations may reflect hypothalamic involvement. This section of the intermediate brain is an endocrine center that regulates the diurnal cycles of various physiological processes in the body.

Purpose of the study: To investigate clinical and neurophysiological characteristics of patients with restless legs syndrome and to determine the influence of the syndrome on the process of chronicization of cerebral circulation disorder.

Material and methods of the study. The most difficult thing was screening and selection of patients, in this connection routine questioning of referred patients to the neurological department, department of X-ray radiology (for diagnostics of ultrasound duplex scanning of leg vessels), department of vascular surgery was carried out. The basis for inclusion in the main group was a complaint of motor night restlessness in the legs. Exclusion or non-inclusion criteria were signs of somatonephrosis, such as severe anemia, chronic renal failure, pregnancy, untreated and uncontrolled high blood pressure, patients with poor glycemic control, smokers, patients with atherosclerotic plaques on carotid arteries, patients with pathology of peripheral neurological disorders and psychiatric disorders. The examined participants were divided and classified by sex (men were twice as many), and age (mean age was 37.5 years), main group: 43 patients. In addition, volunteers without complaints of SBS were selected and included in the comparison group (30) identical in age and gender. For all participants, a standard and modified diagnostic protocol was recommended to evaluate the results, where neurological examination comes first, followed by the necessary laboratory tests of blood biochemistry (coagulogram), neurophysiological studies (electromyography of lower limb muscles), ultrasound

duplex scanning of lower limb vessels (Duplex ultrasound was performed using a Philips duplex ultrasound machine with a frequency range of 5-13 MHz for lower limb arteries). Statistical parameters were studied on an individual computer, using a standard package with the student's method.

Result of the study. On the basis of the set goal, at the first stage of the study we evaluated the number of complaints of SBS, it turned out that of all patients in the main group with SBS, 83% experienced discomfort in the legs both at night and during the day, the remaining percentage is divided into only night restlessness (11%), daytime (6%), and the patients experiencing daytime restlessness of the legs were on average 10 years older than the main average age of the entire group. From the onset of the first signs to the debut of SLE, the history revealed a long interval (on average 5 to 8 years), in addition, all patients indicated a progressive nature of the disease, especially patients experiencing SLE during the day and (in the evening) at night. According to the official classification, SBN is divided into familial and neuropathic and idiopathic (sporadic) forms. The percentage of familial cases of IBD amounted to 47%, which corresponds to the data of various foreign authors. The most interesting was the fact that patients did not apply to doctors directly with the problems of SBS, this sign was revealed in the course of the main complaints (heaviness in the legs, swelling in the evening, impaired walking; memory loss, unexplained anxiety and depression, dizziness, fatigue). Patients described the sensation in the legs by the following signs: the need to change the posture in the legs and urgent desire to move the legs; feeling of "goosebumps", tingling; desire to remove socks, shoes; feeling of pulling discomfort or "as if the legs hardened". All these signs were determined in the majority of the shin (calf muscles) region, occurring deep in the legs. Characteristically, in 33.3% of the patients, SBS manifested with predominance in one or the other leg. Patients felt relief in cases of daytime CPS using walking or arbitrary movements of legs, self-massage of calf muscles, pressing on muscles, or stretching muscles, trying to lift legs (on a chair). In the evening, some patients used foot baths or alcohol compresses. The most difficult to solve the problem was night time, where subjectively sleep was disturbed in 98,5% of patients (having nocturnal SBS), the number of awakenings during sleep reached min 2, max 4 times, at that patient identified some factors (in their opinion, increasing SBS): cold or on the contrary high temperature (heat). Thus, the result of the study analysis revealed that the commonly recognized physical modality that brings relief from SBS is walking. SBS tends to be slowly progressive in most cases, and the pattern of symptoms increases in severity over time, with the mean age of patients with the debut of SBS being statistically significantly lower than the mean age of patients with daytime and nighttime onset (daily manifestation). At the time of the examination from the side of neurological status were determined scattered small focal signs, such as convergence disorder, slight coherence of the nasolabial fold, on one side, slight tongue deviation (in three cases), difference in reflexes on the sides and mainly difference of upper and lower limbs, hypo- or hyperesthesia with difference of sides and with difference of upper and lower limbs. Diagnosis consisted of laboratory, neurophysiological (electromyography), ultrasound vascular duplex scanning, MRI diagnosis of the brain and partial imaging of the legs. Indicators of electroneuromyography (ENMG) were investigated impulse conduction velocity along the tibial and calf nerves, where in 27% of cases a decrease in impulse conduction velocity is noted, with a greater percentage of impaired conduction velocity noted in the calf muscles (58%), tibial muscle (42%) in comparison. Sporadic form is defined in 36% of cases, according to all signs of SBS (many authors combine sporadic cases with familial), it is in these patients, according to ENMG indicators there is no decrease in conduction velocity on the calf and tibial nerves, in addition, there is no hereditary predisposition in the anamnesis and there are no somatic and significant neurological signs .Thus, ENMG in patients with sporadic form on average is: (impulse conduction velocity along the sensitive and motor fibers of the tibial and calf nerve), where the sensitive on the left 54,1 m/s, on the right 52, 1 m/s, on the motor 51,2 m/s on the left, 47, 1 m/s on the right.

Determination of D-dimer level was in 80% of cases, 0.5 μg/mL, at the same time, the index of prothrombin time was within an average of 14 seconds, and the prothrombin index had a level of 83%. The determination of Willebrand factor in plasma was 161%, coagulation factors V, VII, VIII and XII

(87%, 95%, 140%, 100%), as seen by the increase in the level of VIII coagulation factor (140%). This fact is presented as a necessity to control homocysteine plasma levels, analysis of the result showed, in 56% of cases high homocysteine level (15 μmol/L), mostly in males, where ($p<0.01$)in gender ratio. Consequently, the established high level of coagulation factor VIII, in parallel with a reduced level of antithrombin III, high level of Willebrand factor, indicates an increase in thrombogenic activity of the blood and vascular wall. In the study of patients, on the level of lipid spectrum concentration, in the main group, the mean value was above normal (LDL -2.8 mmol/L, HDL, 1.1 mmol/L). In the comparative group (healthy) the level was 0.13±0.01 mmol/l), and high lipid index was noted in 84% of patients, that is, this index is not favorable and most likely a precursor of vascular atherosclerosis, which should be proved by ultrasound examination. Besides, multifocal atherosclerotic disorder with involvement of different vascular basins was characteristic for the examined patients, where in patients with atherosclerotic lesion of lower limb arteries, changes in brachiocephalic vessels were observed in parallel in almost 48% of cases. The study of preconditions and risk factors in the development of peripheral lesions, in particular of the lower extremities, are not less important: gender approach (men are more susceptible), age category (it is interesting that among men it is young age, in women it is older, over 50 years), bad habits (smoking, which was noted in the examined patients of the main group in 98% of men, in 32% of women), increased body weight (obesity of 2-3 degrees, in the study in the main group most patients suffered from increased body weight). Modern protocols of diagnostics of peripheral vascular pathology determination use as a gold standard, ultrasound duplex scanning, in comparison with angiography with the use of computed tomography in the assessment of vascular pathology of the lower extremities, is available, fast and non-invasive (ultrasound duplex, according to many scientists, corresponds to specificity of 95% and sensitivity of 88% for the determination of hemodynamically significant lesions, more than 50% of stenosis and occlusions). Thus, ultrasonic diagnostics was performed in all patients of the main group, and the following results were revealed: partial occlusion (peroneal) in 8 patients; analysis of the results of the hamstring vessels - full occlusion was found in one patient and partial occlusion in 13 patients. As a result, in the total sample stenoses on average higher than 50% of the vessel lumen diameter were determined, femoral artery in 9 patients, hamstring artery - in 10 patients; more than 90% stenosis from the vessel lumen diameter and occlusion of femoral arteries were noted in 5 patients; 2 cases of thrombosis of the segment of the PTBA.

The next stage of the study was the change of clinical, neurological and neuroimaging signs of the examined patients. As it was mentioned above, the patient of the main group had the following complaints: decreased efficiency and vice versa, increased fatigability 50%; memory decline (forgetfulness) 30%; periodic dizziness and headache 43%; sleep disturbance; depression. The complaints became frequent (according to the patients' words, in the last six months), intensified with exertion and decreased with rest. Thus, the complaints of the examined patients were characterized by the presence of cerebrasthenic syndrome. The symptoms of clinical and neurological disorder had scattered small focal character, convergence disorder, facial asymmetry due to smoothing of nasolabial fold, decreased muscle tone in 41,7% (which is an indicator of cerebral atherosclerosis, and corresponds to the literature scientific data). USTCDG of brachiocephalic vessels revealed the following signs in the patients of the main group: “intima-media” complex in the area of common carotid arteries showed in 28,1% compaction (thickening) at the level of 1,3 mm, in the comparison group 0,8 mm; in addition, there is a decrease in the linear velocity of blood flow in the anterior cerebral and middle cerebral arteries (more on the right), in the posterior cerebral and vertebral arteries (more on the left). MRI (brain) neuroimaging was performed in all patients of the main group and in 50 percent of the control group, where almost all patients of the main group (86%) had some or other structural cerebral abnormalities of the brain, moreover, the vascular nature of changes was noted more often than age-related changes. The peculiarity of vascular abnormalities was focal (found in 23% of cases); diffuse and diffuse changes in the area of subcortical white matter (8%) or small focal signs in the area of white matter (11,9%), leukorrheosis was found in 30% of cases (where the main character of the abnormality - periventricular changes), in the general structure many were characterized by

signs of cerebral subatrophy, with a combination of enlargement of subarachnoid space and enlargement of lateral ventricles.

Thus, the example of patients with SBP has shown some of the mechanisms governing this syndrome, emphasizing the importance of changes in large and small vessels, both peripheral and central, that underlie ischemic events and influence their severity. Alterations in endothelial structure itself play a central role in the onset and progression of cerebrovascular disease, and in recent years, many scientists have considered the endothelium as a separate organ, given its volume and function.

When choosing a method of treatment for patients with restless legs syndrome, it is necessary to take into account its cause (primary or secondary nature).

Manifestations of secondary syndrome can be eliminated only after the treatment of the underlying disease that led to the development of the disorder, or filling the identified deficiency. For example, iron preparations should be used for anemia.

In the treatment of mild forms of primary syndrome, non-medication therapy can be carried out. It includes moderate physical activity (focusing on the legs and relaxation), evening walks, massage, rubbing, warmers, warm foot baths. Patients are advised to avoid substances that provoke the appearance of symptoms: nicotine, caffeine and other diuretics, as well as alcohol.

Drug treatment of the syndrome is indicated in severe course of the disorder, sleep disturbance and ineffectiveness of other methods of treatment. It involves taking non-ergotamine dopamine receptor agonists. They make up for the lack of dopamine in the central nervous system.

Pramipexole and levodopa/benserazide are effective agents in all forms of the syndrome. They are used as first-line drugs [2]. Treatment is started with minimal doses. Over time, low doses of pramipexole become insufficient to control symptoms. In such cases, it is possible to increase doses until an effect is achieved or to temporarily change the drug.

If first-line treatment is not possible, second-line treatment with clonazepam, gabapentin or pregabalin may be considered. In severe cases, opioid analgesics and anticonvulsants may be used [4].

Therapy is carried out for a long time (several years). Sometimes treatment is required only during the worsening of the clinical picture. In some cases, drugs are used for life to maintain the remission period [3].

In the treatment of restless legs syndrome during pregnancy, it is recommended to adhere to methods of non-medicamentous therapy, also possible to take folic acid and iron preparations (in case of its deficiency). Drug treatment is possible only in severe course of the disease. In such cases, clonazepam or levodopa is prescribed [1].

Conclusions: Many works are devoted to the relationship of peripheral vascular insufficiency with the development of damage in the blood-brain barrier system, in the subsequent phenomenon of acute cerebral circulatory disorders, exemplified by changes in the endothelial cytoskeleton and conduction velocity and disruption of the blood structure itself, slowly affecting the integrity of the brain structure over time. Active scientific research at the molecular level and the contribution of immune cells and related factors are known to influence the process of destruction of the integrity of the body's vascular system. This obtained information, with the understanding of the pathomechanism of VAS, as one of the causes of lower limb vascular damage with parallel changes in the formation and development of chronic cerebral impairment, should provide therapeutic strategies to preserve vascular integrity, and be an important strategic direction for stroke prevention. Analyzing the results of the study, the significance of some risk factors on cerebrovascular disease, acute stroke and slow brain structure damage, will allow to use the possibility of preventing the occurrence of ischemic events and it will be possible to predict the consequences of the disease.

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