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RISK FACTOR FOR CHRONIC CEREBRAL CIRCULATORY DISORDERS RESTLESS LEGS SYNDROME

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Abstract:

The relationship between the factor of changes in vascular function, autonomic dysfunction in restless legs syndrome and chronicization of cerebral circulation and the pathomechanism underlying these relationships remains unclear and debatable. By the method of clinical and neurological symptoms, instrumental and using questionnaires (scales), we have shown that restless legs syndrome affects the mechanism of regulation of changes in large and small vessels, both peripheral and central, which underlie ischemic events and influence their severity. At the same time, changes in endothelial structure 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, taking into account its volume and function. The result of the obtained analysis, 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 cerebrovascular impairment, should provide therapeutic strategies to preserve vascular integrity, and be an important strategic direction for stroke prevention.

Keywords: CNMC, SBN, Clinical and neurologic symptoms, TDS ultrasound, ENMG, MRI.

INTRODUCTION. Recently, a very commonly used definition is "restless legs syndrome" (RLS), which at first glance seems to be non-medical. In the early 17th century, the syndrome was described by Thomas Willis, an English physician-physiologist. In 1861, the German physician Theodor Witmack continued to study this problem. A more detailed clinical and neurological study of the state of WLS in 1944 was conducted by Swedish neurologist Karl-Axel Ekbom, in this regard, the syndrome is treated as, Willis-Ekbom disease or Witmak-Ekbom syndrome. Restless legs syndrome (RLS) is a fairly common neurologic sensorimotor change, associated with sensory discomfort, exacerbated at night (painful sensation in the legs, causing an overwhelming need to move the legs) or with inactivity (in an airplane). Allen R.P. et al. (2015) and Janes F. et al. (2021), in their studies, divided SLE into primary (idiopathic) and secondary, taking into account the comorbid background (anemia-iron deficiency, CKD, peripheral nervous system disease, intoxication from medications or micronutrient deficiencies, etc.). [1, 5, 9, 13]. In addition, SBN is referred to the group of diseases, the fundamental emphasis of which is considered to be motor dysfunction, the question of the functional state of segmental and suprasegmental structures that provide coordination of reflex activity of the locomotor system remains debatable (Chamsaem M.A., 2004). The search of scientific literature sources, showed the main signs and factors of the disease, but only a few researchers connect cerebral circulation disorder with SBN, for example, with the problem of subcortical and stem lesion foci, where quite complex pathogenetic interrelationships between multimedia neurochemical pathways in SBN are considered [4, 6, 10, 12]. Thus, Lanza G. et al. (2019), dysfunctionality in the legs is determined by genetic predisposition and exogenous factors (comorbidities: arterial hypertension, cardiovascular insufficiency, obstructive sleep apnea). Such an explanation between SBN and SSN, give the method of vascular scanning (breath-hold test, reactivity of intracranial vessels in response to the stimulus of respiratory change), which visually indicate vasomotor reactivity in the percentage change in blood flow velocity in response to changes in carbon dioxide content, which in turn works as a strong vasodilator (Sloan M.A., Alexandrov A.V., 2009). What is the relationship between changes in vascular function, autonomic dysfunction and SBH, the pathomechanism underlying this relationship remains unclear, perhaps the syndrome enhances atherosclerosis, or conversely a high level of peripheral vascular lesions with

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atherosclerosis, worsens the vascular response, which in turn leads to a higher susceptibility to vascular risk factors themselves [3, 7, 11]. In addition, the lack of conclusive data to identify the causes of the disease, make it difficult to treat the syndrome. Abramovskikh L.E. (2019), in his work raises the problem of sleep disorders and considers the key factor of SBN, where he notes that insomnia in turn leads to depression, combined, increases the risk of CVD, and it turns out that SBN more often than in the population develops brain stroke. According to Russian scientists, the incidence of SSN is associated with polyneuropathies of various genesis, radiculopathies, venous insufficiency, or Parkinson's disease [2, 8, 12, 14].

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

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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 (Fig. 1); significant hemodynamic internal problem (intima lesion) was noted in one patient.

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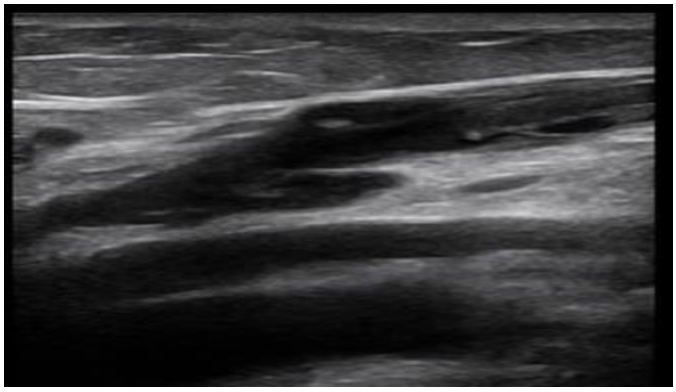

Figure 1. Thrombosis of the saphenous and small saphenous vein on the right side with a doppler.

Figure 2. Thrombosis of the right saphenous and small saphenous veins

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 (Fig. 3).

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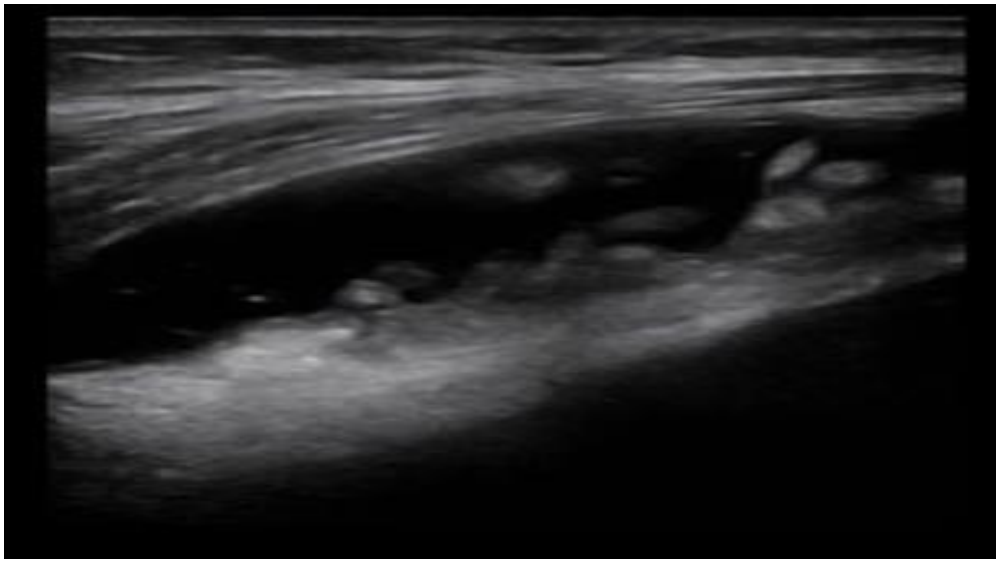

Figure 3. Baker cyst

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.

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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