

THE EFFECT OF RESTLESS LEGS SYNDROME ON CEREBRAL ISCHEMIC EVENTS

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Abstract: Recently, a very commonly used definition is "restless legs syndrome", which at first glance does not seem to be medical.

Key words: Restless legs syndrome, ischemia, brain.

Introduction. At the beginning of the XVII century, the syndrome was described by Thomas Willis, an English physiologist. In 1861, the German physician Theodor Witmak continued to study this problem. A more detailed clinical and neurological study of the condition "restless legs syndrome" in 1944 was conducted by the Swedish neurologist Karl-Axel Ekbom, in this regard, the syndrome is interpreted as Willis— Ekbom disease or Witmak— Ekbom syndrome. Restless legs syndrome is a fairly common neurological sensorimotor change associated with sensitive discomfort, which worsens at night (painful sensation in the legs, causing an irresistible need to move the legs) or when inactive (on an airplane). Allen R.P. et al. (2015) and Janes F. et al. (2021), in their research, they divided the "restless legs syndrome" into primary (idiopathic) and secondary, taking into account the comorbid background (anemia-iron deficiency, CRF, peripheral nervous system disease, intoxication from taking medications or lack of trace elements, etc.D.) (1, 5, 9, 13). In addition, "restless legs syndrome" is classified as a group of diseases, the fundamental focus of which is motor dysfunction, the question of the functional state of segmental and suprasegmental structures that coordinate the reflex activity of the locomotor system remains debatable (Chamsai M.A., 2004). The search for scientific literature sources has shown the main signs and factors of the disease, but only a few researchers associate a violation of cerebral circulation with "restless legs syndrome", for example, with the problem of subcortical and stem lesions, where rather complex pathogenetic relationships between multimedia neurochemical pathways in "restless legs syndrome" are considered (4, 6, 10, 12). So, Lanza G. et al. (2019), dysfunctionality in the legs is determined by genetic predisposition and exogenous factors (concomitant diseases: hypertension, cardiovascular insufficiency, obstructive sleep apnea). Such an explanation between "restless legs syndrome" and SSN is given by a vascular scanning method (breath retention test, intracranial vessel reactivity in response to a stimulus of respiratory change), which visually indicate vasomotor reactivity in percentage changes 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, violation of the autonomic system and "restless legs syndrome", the pathomechanism underlying these relationships remains unclear, perhaps the syndrome increases atherosclerosis, or vice versa, a high level of peripheral vascular damage by 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 convincing data on the identification of the causes of the disease makes it difficult to treat the syndrome. Abramovskikh L.E. (2019), in his work

raises the problem of sleep disorders and considers the "restless legs syndrome" to be a key factor, where he notes that insomnia, in turn, leads to depression, combined, increases the risk of CNS, while it turns out that "restless legs syndrome" develops a brain stroke more often than in the population. According to Russian scientists, the incidence of "restless legs syndrome" is associated with polyneuropathies of various origins, radiculopathy, venous insufficiency, or Parkinson's disease (2, 8, 12, 14). Thus, the study of the course of various forms of "restless legs syndrome", a differentiated approach to diagnosis, the study of complications and the relationship with chronic cerebrovascular accident and acute circulatory disorder is relevant.

The purpose of the work. To study the clinical and neurophysiological characteristics of patients with restless legs syndrome and to determine the effect of the syndrome on the process of chronization of cerebral circulatory disorders.

Research materials and methods. Screening and selection of patients turned out to be the most difficult, in connection with this, a routine survey of patients referred to the neurological department, the department of X-ray radiology (for the diagnosis of Ultrasound duplex scanning of leg vessels), the department of vascular surgery was conducted. The reason for inclusion in the main group was a complaint of motor nocturnal restlessness in the legs. The exclusion or non-inclusion criteria were signs of somatonic insufficiency, such as severe anemia, chronic renal failure, pregnancy, untreated and uncontrolled high blood pressure, patients with poor glycemic control, smokers, with atherosclerotic plaques on the carotid arteries, patients with pathology, peripheral neurological disorders and mental abnormalities. The examined participants were divided and classified by gender (there were twice as many men) and age (the average age was 37.5 years), the main group: 43 patients. In addition, volunteers without complaints of "restless legs syndrome" were selected, who entered the comparison group (30) identical in age and gender. A standard and modified diagnostic protocol is recommended for all participants to evaluate the results, where a neurological examination comes to the fore, followed by the necessary laboratory tests of blood biochemistry (coagulogram), neurophysiological studies (electromyography of the muscles of the lower extremities), ultrasound duplex scanning of the vessels of the lower extremities (Duplex ultrasound was performed using a Philips duplex ultrasound machine with a frequency range of 5-13 MHz for the arteries of the lower extremities). Several patients underwent MRI of the lower extremities and in 100% of cases, MRI of the brain. Statistical indicators were studied on an individual computer using a standard package using the Student's method.

Result of investigation. Based on this goal, at the first stage of the study, an assessment was made on the number of complaints of "restless legs syndrome", it turned out that of all patients in the main group with "restless legs syndrome", 83% experienced discomfort in their legs both at night and during the day, the remaining percentage was divided into only night anxiety (11%), daytime (6%), and patients experiencing daytime leg restlessness were on average 10 years older than the main average age of the entire group. From the beginning of the first signs to the debut of "restless legs syndrome", according to the anamnesis, a long period was revealed (on average from 5 to 8 years), in addition, all patients indicate the progressive nature of the disease, especially for patients experiencing "restless legs syndrome", during the day and (evening) at night. According to the official classification, "restless legs syndrome" is divided into familial and neuropathic and idiopathic (sporadic) forms. The percentage of family cases of "restless legs syndrome" was 47%, which corresponds to the data from the works of various foreign authors. The most interesting thing was the fact that patients did not go to doctors directly with the problems of "restless legs syndrome", this sign was revealed during the main complaints (heaviness in the legs, swelling in the evening, impaired walking; memory loss, unexplained anxiety and depression, dizziness, fatigue). The sensation in the legs was described by patients with the following signs: the need to change the position in the legs and an urgent desire to move the legs; a feeling of "goosebumps", tingling; a desire to take off socks, shoes; a feeling of pulling discomfort or "as if the legs had hardened". All these signs were detected in the majority of the shin area (calf muscles), arising in the depth of the legs. It is characteristic that in 33.3% of patients, the "restless legs syndrome" manifested itself with a predominance in one or the other leg. Patients felt

relief, in cases of daytime "restless legs syndrome" using walking or voluntary foot movements, self-massage of the calf muscles, pressing on the muscles, or stretching the muscles, they tried to lift their legs (on a chair). In the evening, some patients used foot baths or alcohol compresses. The most difficult solution to the problem was noted at night, where sleep was subjectively disrupted in 98.5% of patients (with nocturnal "restless legs syndrome"), the number of awakenings during sleep reached min 2, max 4 times, while patients identified some factors (in their opinion, exacerbating the "restless legs syndrome"): cold or vice versa high temperature (heat). Thus, the result of the analysis of the study revealed that walking is a generally significant physical method that brings relief from "restless legs syndrome". "restless legs syndrome" tends to progress slowly in most cases, and over time, the nature of symptoms increases in severity of symptoms, while the average age of patients with the onset of "restless legs syndrome" is statistically significantly less than the average age of patients with daytime and nighttime symptoms (daily manifestation). At the time of examination, scattered small focal signs were determined from the neurological status, such as a violation of convergence, slight coherence of the nasolabial fold, on one side, slight deviation of the tongue (in three cases), a difference in reflexes on the sides and mainly the difference of the upper and lower extremities, hypo- or hyperesthesia with a difference of sides and with a difference upper and lower extremities. The diagnosis consisted of laboratory, neurophysiological (electromyography), ultrasound duplex scanning of blood vessels, MRI diagnostics of the brain and partial visualization of the legs. Indicators of electroneuromyography (ENMG) studied the pulse conduction rate along the tibial and calf nerves, where in 27% of cases there was a decrease in the pulse conduction rate, while a greater percentage of impaired conduction velocity was noted in the calf muscles (58%), tibial muscle (42%) in comparison.

The sporadic form was determined in 36% of cases, according to all signs of "restless legs syndrome" (many authors combine sporadic cases with family ones), it is in these patients that, according to ENMG indicators, there is no decrease in the rate of conduction along 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, the average ENMG in patients with sporadic form is: (the rate of pulse conduction along the sensitive and motor fibers of the tibial and calf nerves), where on the sensitive 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.

Table 1. Analysis of the results of ultrasound duplex scanning of patients in the main group

Indicators	Vps (BA) cm/s	Vps (PKA) cm/s	Vps (BBA) cm/s	LPI
The main group	52,2±10,1	33,0±5,0	22,9±6,1	0,3±0,08
The Control Group	70,2±9,99	53,8±6,35	38,8±12,5	0,9±0,01

где, $p \geq 0,0001$

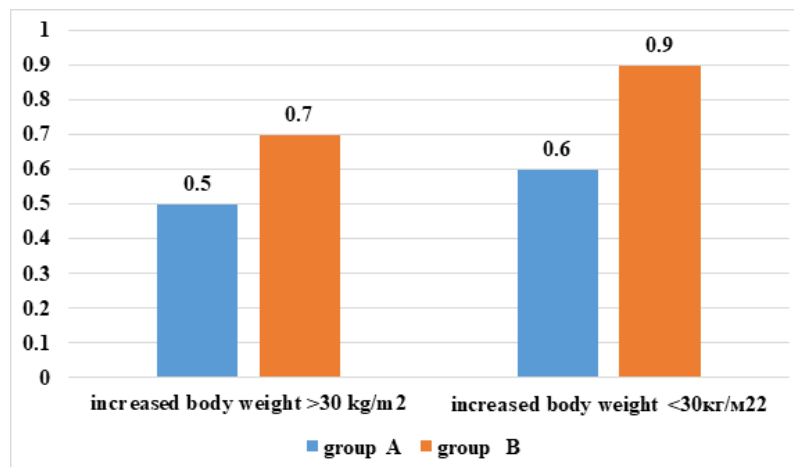


Fig.1 Indicators of ultrasound duplex scanning in patients of the main group with increased body weight (PMT), where, $rB0.05$ relative to patients with increased body weight

Table 2. Diagnostic sensitivity, specificity and effectiveness of score scale indicators in patients with SDS (n=31)

Indicator	Se (%)	Sensitivity Sp (%)	Effectiveness
Change in arterial pulsation there is no pulsation in the popliteal region and on the foot	96,56%	50%	72%
White blood cells (X 10 ⁹ /l) above 10.5	74%	36%	50%
ESR (mm/h) above 34.6	50%	74%	68%
LVSL (mmol/l) above 0.16	60%	73%	66%
Degree of stenosis - stenosis from 70% to 100%	13,5%	98%	55%
	90%	66%	79%
LSC (cm/s) - 10.0	33%	100%	66%
LPI - 0.6	10%	100 %	50%

Table 3. The nature of clinical and neurological characteristics of patients in the main group (%)

Indicators	The main group	The control group
	До лечения	После лечения
Leg soreness at rest (in sleep)	100	0
Tap and cramps in the calf muscles	79,5	0
Heaviness, fatigue in the muscles of the shins	36,6	2,1
Impaired sensitivity of the skin of the lower extremities	68	2
Cold feet, Chilly feet	90	3
Violation of the shin covering, thinning and dry skin	60	1,9
Deformation of the nail plates		

***p<0.05 - the reliability of differences in relation to the control group, #p<0.05 - the reliability of differences in relation to the UNCP group**

Assessing the hemostasis parameters (coagulograms) in the examined patients with "restless legs syndrome", the average range of values was noted within relatively normative limits: the fibrinogen level was within 3.5 g/l, the thromboplastin time was within 38 seconds, the fibrinolytic activity of blood plasma (fibrinolytic index) was 17%, the analysis of antithrombin III was 95%. The determination of the D-dimer level turned out to be in 80% of cases, 0.5 mcg/ml, at the same time, the prothrombin time index was within an average of 14 seconds, and the prothrombin index at the same time had a level of 83%. The determination of Willebrand factor in blood plasma was 161%, coagulation factors V, VII, VIII and XII (87%, 95%, 140%, 100%), as can be seen, an increase in the level of coagulation factor VIII (140%). This fact is presented as the need to control homocysteine levels in blood plasma, the analysis of the result showed, in 56% of cases, a high level of homocysteine (15 mmol /l), mainly in men, where (p<0.01) in the gender ratio. Consequently, the established high level of coagulation factor VIII, in parallel, a reduced level of antithrombin III, a high level of Willebrand factor, indicates an increase in thrombogenic activity of the blood and vascular wall. In the study of patients, the level of lipid spectrum concentration in the main group, the average value was higher than 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), while a high lipid index was noted in 84% of patients, that is, this indicator is not favorable and most likely a harbinger of vascular atherosclerosis, which should be proved by ultrasound examination. In addition, a multi-focal atherosclerotic disorder involving various vascular basins turned out to be characteristic of the examined patients, where in patients with atherosclerotic lesion of the arteries of the lower extremities, changes from the brachiocephalic vessels were observed in parallel in almost 48% of cases. It is not unimportant to

study the prerequisites and risk factors in the development of peripheral lesions, in particular of the lower extremities, this is a gender approach (men are more susceptible), age category (interestingly, this is a young age among men, older in women, over 50 years old), bad habits (smoking, which was noted in the examined patients in the main group, 98% in men, 32% among women), increased body weight (obesity 2-3 art., in the study in the main group, most patients suffered from increased body weight). Modern diagnostic protocols for determining peripheral vascular pathology are used as the gold standard, ultrasound duplex scanning, in comparison with angiography using computed tomography in assessing vascular pathology of the lower extremities, is affordable, fast and non-invasive (duplex ultrasound, according to many scientists, corresponds in specificity to 95% and sensitivity to 88% for determining hemodynamically significant lesions, more than 50% of stenosis and occlusion). Thus, ultrasound diagnostics was performed in all patients of the main group, with the following results: partial occlusion (fibula) in 8 patients; analysis of the results of popliteal vessels - complete occlusion was found in one patient and partial occlusion in 13 patients. As a result, in the general sample, stenoses were determined on average above 50% of the diameter of the vessel lumen, femoral arteries in 9 patients, popliteal artery in 10; more than 90% of stenosis from the diameter of the vessel lumen and occlusion of the femoral arteries were noted in 5 patients; 2 cases - thrombosis of the CHTB segment (Fig. 2); significant hemodynamic internal problem (intimal lesion) it was noted in one patient.

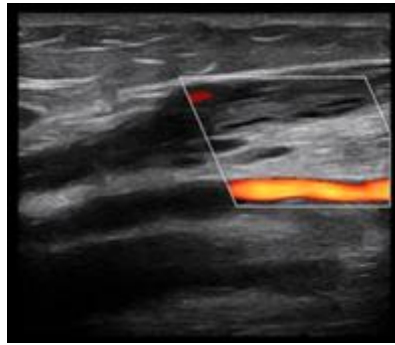


Fig. 3. Thrombosis of the popliteal and small saphenous veins on the right with a Doppler.

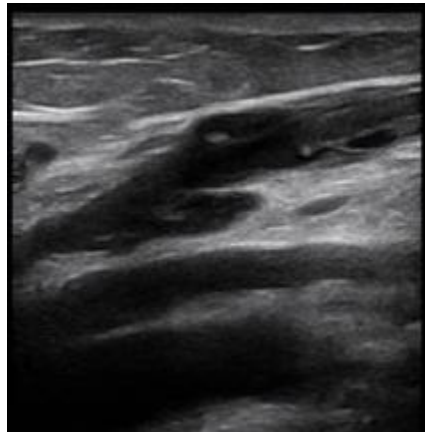


Fig. 4. Thrombosis of the popliteal and small saphenous veins on the right

The next stage of the study was to change the clinical, neurological and neuroimaging characteristics of the examined patients. As noted above, the patient in the main group had the following complaints: decreased performance and vice versa, increased fatigue by 50%; decreased memory (forgetfulness) by 30%; periodic dizziness and headache by 43%; sleep disturbance; depression. Complaints have become frequent (according to patients, in the last six months), increase with exercise and decrease with rest. Thus, the complaints of the examined patients were characterized by the presence of cerebrastronic syndrome. The symptoms of the clinical and neurological disorder had a diffuse small focal character, impaired convergence, facial asymmetry due to smoothness of the nasolabial fold, decreased muscle tone by 41.7% (which is an indicator of cerebral atherosclerosis, and corresponds to

literary scientific data). Ultrasound examination of brachiocephalic vessels revealed the following signs in patients of the main group: the intimamedia complex in the area of the common carotid arteries showed in 28.1% a 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 through the anterior cerebral and middle cerebral arteries (more on the right), along the posterior cerebral and vertebral arteries (more on the left). Neuroimaging by MRI (brain) was performed in all patients of the main group and in 50 percent of the control group, where almost all of the examined main group (86%) had some kind of structural cerebral abnormalities of the brain, in addition, the vascular nature of the changes was noted more often than age-related changes. A feature of vascular disorders was focality (found in 23% of cases); diffuse-diffuse index of changes in the subcortical white matter area (8%) or small focal signs were noted in the white matter area (11.9%), leukorrhea was detected in 30% of cases (where the main character of the disorder is a periventricular change), in the general structure, many were characterized by signs of subatrophy of the brain, with a combination of an increase in the subarachnoid space and expansion of the lateral ventricles (fig. 5).

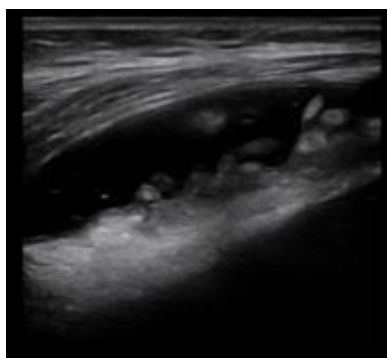


Fig. 5. Baker's cyst

Thus, using the example of patients with "restless legs syndrome", some mechanisms regulating this syndrome were shown, where emphasis was placed on the importance of changes in large and small vessels, both peripheral and central, which underlie ischemic events and affect their severity. By itself, a change in the structure of the endothelium plays a central role in the occurrence and progression of cerebrovascular diseases, and in recent years, many scientists have considered the endothelium as a separate organ, taking into account its volume and function. A lot of works are devoted to the connection of peripheral vascular insufficiency with the development of damage in the blood-brain barrier system, followed by the phenomenon of acute cerebral circulatory disorders, for example, changes in the endothelial cytoskeleton and the rate of conduction and disorders of the blood structure itself, a slow effect on the integrity of the brain structure over time. Active scientific research at the molecular level and the contribution of immune cells and related factors influencing the process of destruction of the integrity of the vascular system of the body are known.

Conclusions: This information obtained, with an understanding of the pathomechanism "restless legs syndrome" as one of the causes of vascular damage in the lower extremities with parallel changes in the formation and development of chronic cerebral impairment, should provide therapeutic strategies to preserve the integrity of blood vessels, and be an important strategic direction for stroke prevention. The analysis of the results of the study, the significance of some risk factors for cerebrovascular diseases, acute stroke and slow damage to the brain structure, will allow using the opportunity to prevent the occurrence of ischemic events and it will be possible to predict the consequences of the disease.

Literature

1. Stephen K. Van Den Eeden, Kathleen B. Albers, Julie E. Davidson, Clete A. Kushida, Amethyst D. Leimpeter, Lorene M. Nelson, Rita Popat, Caroline M. Tanner, Kristen Bibeau, Charles P. Quesenberry Risk of Cardiovascular Disease Associated with a Restless Legs Syndrome Diagnosis

- in a Retrospective Cohort Study from Kaiser Permanente Northern California // *Sleep*, 2015, № 7 (38), p. 1009–1015
2. Hu X., De Silva T.M., Chen J., Faraci F.M. Cerebral Vascular Disease and Neurovascular Injury in Ischemic Stroke. // *Circulation research*, 2017. 120(3), 449–471
 3. Lamberti, N., López-Soto, P. J., Rodríguez-Borrego, M. A., Straudi, S., Basaglia, N., Zamboni, P., Manfredini, R., Manfredini, F. Restless Leg Syndrome in Peripheral Artery Disease: Prevalence among Patients with Claudication and Benefits from Low-Intensity Exercise. // *Journal of clinical medicine*, 2019. № 8(9), 1403.
 4. Ко С.Ю., Ким М.С., Ли С.М., Хонг Дж.М., Юн Дж.Х. Нарушение функции сосудистого эндотелия у пациентов с синдромом беспокойных ног: новый аспект сосудистой патофизиологии. *Дж. Нейрол. наук.* 2015 г.; 359: 207–210. doi: 10.1016/j.jns.2015.10.041.
 5. Gao X., Ba D.M., Bagai K., Liu G., Ma C., Walters A.S. Treating Restless Legs Syndrome Was Associated With Low Risk of Cardiovascular Disease: A Cohort Study With 3.4 Years of Follow-Up. // *Journal of the American Heart Association*, 2021. 10(4), e018674. <https://doi.org/10.1161/JAHA.120.018674>
 6. Dzhurabekova Aziza Takhirovna, & Shaymatov Rakhmonberdi Uktamovich. DIAGNOSTICS AND TREATMENT OF CHRONIC CEREBRAL CIRCULATORY DISORDERS AGAINST THE BACKGROUND OF DIABETES MELLITUS. // *The American Journal of Medical Sciences and Pharmaceutical Research*, 2023. № 5(05), p. 42–48.
 7. Jurabekova Aziza Takhirovna, Shmyrina Ksenia Vladimirovna, & Vyazikova Natalia Fedorovna. A COMPREHENSIVE APPROACH TO THE DIAGNOSIS OF IMPAIRED WALKING IN PATIENTS WITH DYSCIRCULATORY ENCEPHALOPATHY. // *World Bulletin of Public Health*, (2023). 19, 13-17. Retrieved from <https://scholarexpress.net/index.php/wbph/article/view/2111>
 8. Salminen A.V., Rimpilya V., Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease) *Neurology*. 2014; 82 : 1856-1861.
 9. Lanza G., Bachmann K.G., Goraeb I., Wang Yu., Ferry R., Paulus V. Excitability of the central and peripheral nervous system in restless legs syndrome. *Dream Med.* 2017; 31 :49-60.
 10. Tardov M.V., Burchakov D.I. Differential diagnosis of disorders of lower limb movements in sleep in adults // https://umedp.ru/articles/differentsialnaya_diagnostika_narusheniy_dvizheniy_nizhnikh_konechno_stey_vo_sne_u_vzroslykh.html
 11. Buzunov R.V., Tsareva E.V. RESTLESS LEGS SYNDROME // *Textbook for doctors*, Moscow 2011, 32 p.
 12. Lyubimov A.V., Cefranova Zh.Yu. The relevance of restless legs syndrome in the daily practice of a neurologist. // *Actual problems of medicine*, 2012. 17 (4 (123)), pp. 273-279.
 13. Kovalchuk M.O., Kalinkin A.L. Restless legs syndrome: pathogenesis, diagnosis, treatment. Literature review. // *Neuromuscular diseases*, 2012. (3), pp. 8-20.