

## FEATURES OF CLINICAL AND HEMODYNAMIC COURSE OF CHRONIC MIGRAINE. ANALYTICAL APPROACH

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### ABSTRACT

According World Health Organization (2012), migraine is one of the top 40 serious conditions cause disability in the world, as well as stroke, meningitis, epilepsy, and, according to some data, cause a significant economic burden to society and the state as a whole. The purpose was to study the clinical, pathophysiological and hemodynamic features of the course of chronic migraine. 82 patients with chronic migraine were studied, aged 12 to 47 years; the average age was  $31,9 \pm 3,8$  years. For comparison, 85 patients with simple migraine (migraine without aura) were selected, aged 14 to 42 years, and their average age was  $29,2 \pm 2,6$  years. The following analysis were carried out: clinical, neurological, electroencephalographic, and

hemodynamic studies, the ID-migraine questionnaire, MIDAS scale (with the determination of migraine severity), EEG, and cerebral vascular ultrasound. Clinical and neurological, bioelectric and hemodynamic features of chronic migraines have been identified – prolonged migraine paroxysms, intense headaches, reduced performance, daily work activity lead to deterioration of the condition and form psychopathological manifestations, reduce the quality of life; EEG parameters can be objective indicators of the development of acute and chronic vascular complications, determining organic brain damage; migraine paroxysms are the background for the violation of the quality abilities of the cerebral vessels, and the frequency and duration of attacks change the normal physiology of the cerebral blood supply to the brain, being a predictor of acute and chronic brain ischemia.

**KEYWORD:** *migraine, chronic migraine, ID-migraine questionnaire, MIDAS scale, EEG, ultrasonic dopplerography.*

## Relevance

According World Health Organization (2012), migraine is one of the top 40 serious conditions [Sacco S. et al, 2013] that cause disability in the world population, as well as stroke, meningitis, epilepsy, and, according to some data, cause a significant economic burden to society and the state as a whole [Berg J. et al, 2005; Burch R. C et al, 2015].

By studying the problem of migraine, we were convinced of the complexity of etiopathogenesis and the presence of various theories regarding the formation of its complicated forms. One of the theory is a biochemical one, which states the hypoactive cell membrane due to decreased level of serotonin in the blood, which cause pulsating headache. The predominance of migraine attacks in women says the opposite – changes in the level estrogens in plasma increases the content of serotonin [Ripa P. et al, 2014].

Akerman S. (2011) and colleagues found in their research that the level of platelet catecholamine – norepinephrine in migraines without aura is higher than in migraines with aura, and the level of platelet epinephrine and dopamine remain the same. In the results of Amoozegar's study (2015) and American Headache Society (2019) showed a decrease in serotonin release from platelets only in patients with migraine with aura [Kondratev A.V., 2017; Sanoeva M. Zh.et al, 2016].

Another and the dominant theory of the development of migraine is trigeminovascular. This theory is based on a vicious circle between the extra - and intracranial vessels, the trigeminal nerve, and the central nervous system. So, control of cerebral membranes (hard and soft) is carried by the trigeminal nerve, irritation of which leads to the imbalance of the pathochemical mechanisms and deactivation of the central nervous system with the development of the "creeping depression", highlighting – vasoactive peptides (neurokinin A, substance P, etc.), then there happens extravasation of protein, degranulation of mast cells and platelet activation, with development of perivascular edema of the brain vessels and aseptic neurogenic inflammation of meningeal vessels that cause paroxysmal headache [S. Akerman et al, 2005; S. K. Aurora et al, 2007].

An important role is played by the state of the autonomic nervous system (ANS). According to the research by A. M. Wein et al. (2001) and V. V. Osipova (2015), the pathogenesis of migraine involves not only segmental parts of the brain, but also excessive cerebral adrenergic activation (dysfunction of noradrenergic innervation of intra - and extracerebral

vessels), which causes the phenomenon of sympathetic denervation hypersensitivity of vascular receptors, and logically, become the cause of vasoconstriction, a decrease in blood supply systems, followed by uneven expansion of vascular walls, neurovascular disorder CNS and formation of hypoxic ischemia of brain areas [Osipova V. V. et al, 2012].

Summing up the complex pathophysiological concept, it is necessary to take into account that migraine is a significant disease for humanity, accompanied by serious complications such as disorders of the functioning of cerebral integrative vascular and neuronal mechanisms that lead to the interaction of the adaptive and antinociceptive systems with the development of inflammatory reaction of the vascular wall, perivascular edema and ischemic cascade of focal and/or diffuse localization of hypoxic nature of the lesion and, accordingly, have set the goal to study the clinical, pathophysiological and hemodynamic features of chronic migraine in patients.

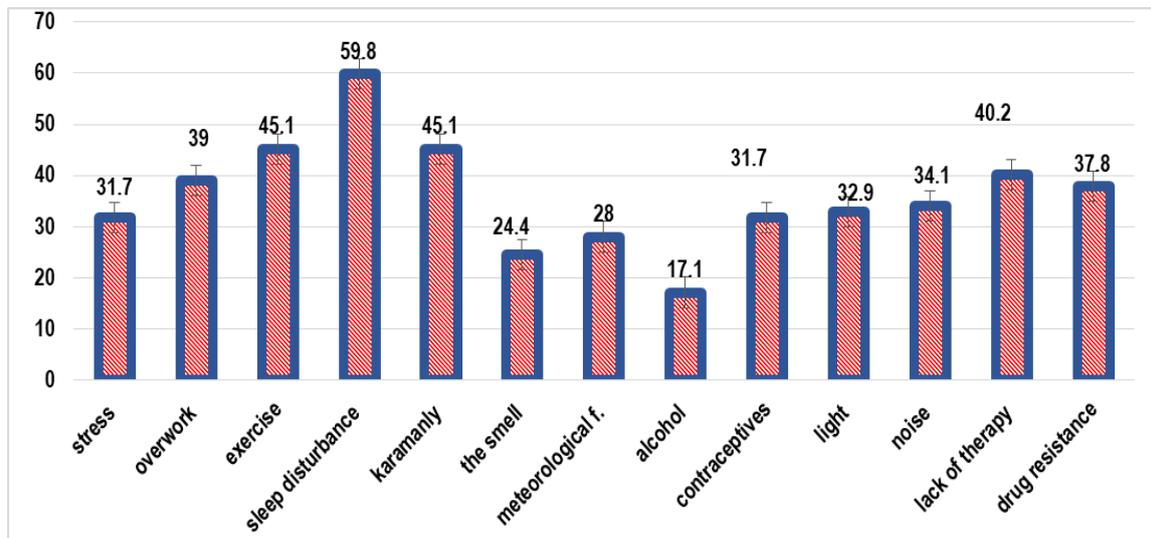
## **MATERIAL AND METHODS**

We studied 82 patients with chronic migraine, aged 12 to 47 years; the average age was  $31,9 \pm 3,8$  years. As a comparison group, we selected 85 patients with simple migraine, aged 14 to 42 years; the average age was  $29,2 \pm 2,6$  years. The following examinations were carried out: clinical, neurological, electroencephalographic, hemodynamic studies, ID-migraine questionnaire, the MIDAS scale (with the definition of migraine severity), EEG, and cerebral vascular ultrasound.

## **RESULTS**

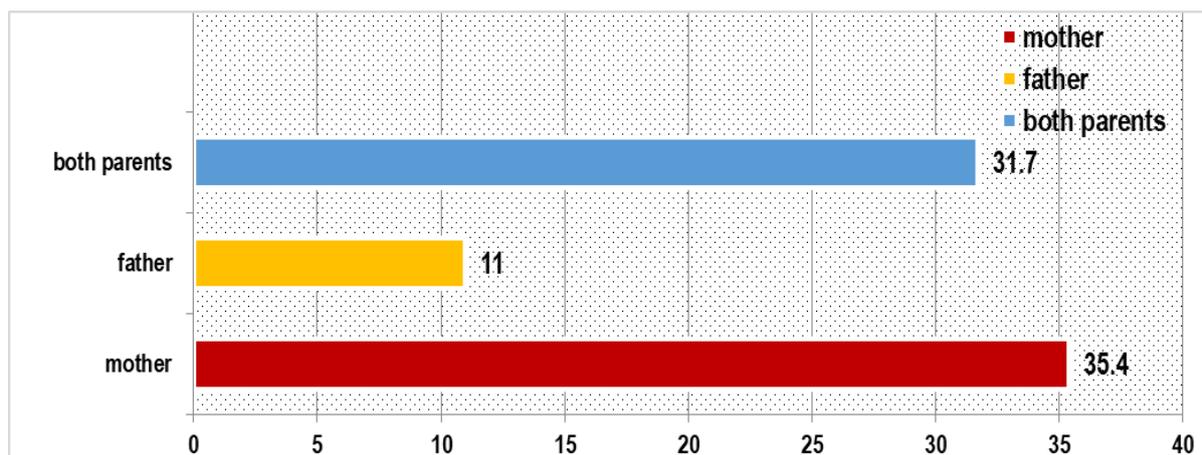
The duration of the disease in patients with chronic migraine varied from 7 to 27 years. It was found that the severity of the clinical course of migraine was inversely proportional to the duration of the disease and the age of patients. Thus, with a disease history of more than 10 years, the risk of developing vascular complicated forms increased by 2.6 times, while the older the patient's age, the easier it was to tolerate a migraine attack, despite the existing vascular deficit, and at a younger age, with a less long history of attacks were more difficult, both in psychological and physical terms. The proof of this was a reliably long history of the disease, a long period of attacks (up to 21 days, often without light intervals). The frequency of attacks in chronic migraine was  $4,7 \pm 0,7$  times every 3 months. Light intervals had a significantly short period, amounting to  $4,6 \pm 0,7$  days, in contrast to uncomplicated forms of migraine ( $P < 0.05$ ).

Among the provoking factors, physical exertion, sleep disturbance, catamenal factor, lack of adequate therapy, and resistance of migraine attacks to therapy were prevalent (Fig. 1).



**Fig. 1** Factors that provoke attacks of chronic migraine.

The female line played a large role in the hereditary factor, fathers suffering from migraine headaches were 2.4 times less than mothers with migraines ( $P > 0.005$ ). However, in patients whose both parents suffered from migraines, aura attacks and hemicranias were observed twice as often ( $P > 0.05$ ), more severe and longer than in patients who suffered from one parent (Fig. 2).



**Fig. 2** Hereditary burden of patients with chronic migraine.

The analysis of cause-and-effect factors of chronic migraine confirmed the polyethologicity and polymorphism of its pathogenesis, and exogenous and endogenous factors had a great

influence in the formation of attacks. Attention was drawn to the fact that exogenous factors prevailed in uncomplicated forms, while endogenous factors prevailed in chronic migraines.

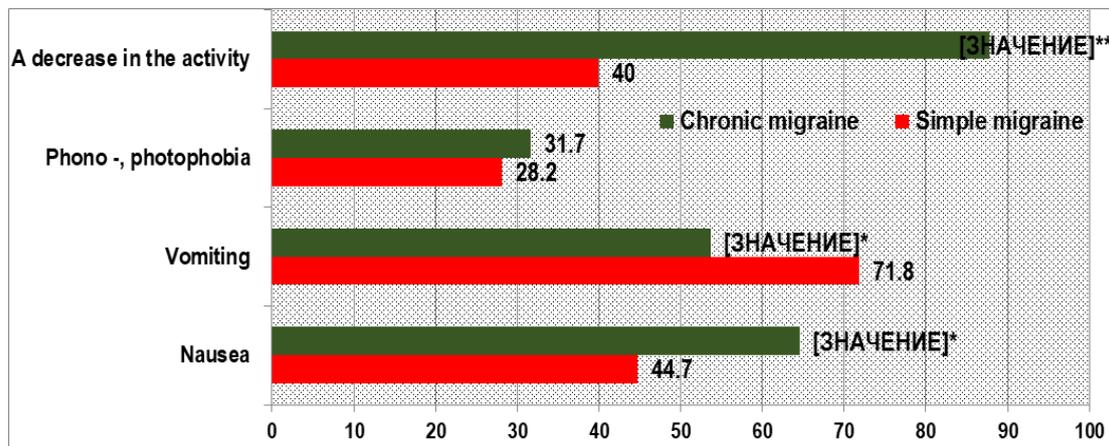
Migraine with aura was observed in 32 (39.0%) patients with chronic migraine, which lasted up to 35 minutes. Patients suffering from migraines with aura (MA) of childhood were characterized by the longest aura (up to 40-50 minutes), in the form of visual-sensory symptoms – Alice in Wonderland syndrome, 8.6% of children who had generalized convulsions with loss of consciousness had migraines with aura, and almost always the convulsions developed against the background of intense attacks of hemicranias. The presence of aura was 3 times more prevalent than uncomplicated forms of migraine ( $P < 0.05$ ).

The ID-migraine questionnaire assessed the main complaints of patients, such as nausea and vomiting, intolerance to light and sound, restriction of working capacity, study or daily activity for at least one day against the background of headaches. The questionnaire was analyzed for the last 3 months of treatment. The questionnaire allowed us to quantify the impact of subjective data on the physical and emotional state of the patient, which was particularly helpful for dynamic control over the course of treatment [Sanoeva M. Zh. et al, 2019].

Chronic migraines due to prolonged migraine paroxysms were more difficult to bear, and the attacks, starting with a pressing character, increased to an intense pulsating one by 5-6 days. Multiple vomiting was 2 times more prevalent in the group of patients with uncomplicated migraines ( $P < 0.05$ ). Children suffering from migraines, both with uncomplicated and chronic migraines, suffered nausea and vomiting much more severely than in other age groups ( $P < 0.05$ ), vomiting was mainly repeated, did not bring relief, and after stopping passed to the urge to vomit.

Patients due to intolerance to light and sound became anxious, agitated, aggressive, lost appetite, hyperosmia was observed – they could not stand the smell of food, spices and perfumes, which increased the headache. The attacks led to a sharp decrease in performance and daily activity, which were the main symptom of patients with chronic migraines prevailing group with uncomplicated migraines 2 times ( $p < 0.05$ ), in the majority (53.5%) of patients, it lasted for 3-5 days. After relief of migraine paroxysm-patients noted General lethargy, a feeling of heaviness and fatigue throughout the body, as well as drowsiness.

Nausea in chronic migraines was often combined with short-term systemic vertigo, which passed after deep sleep and taking NSAIDs. Comparing the indicators of ID-migraine, along with the classic symptoms revealed hyperosmia, hypersalivation, systemic vertigo, heaviness in the head during migraine attacks, restless legs syndrome, which were characterized by persistence and duration. In contrast to the main group in the comparison group, vomiting brought relief – headaches decreased, nausea stopped, the post-seizure period was easier for patients, and it ended within 3 to 6 hours. The psychoemotional background was more stable in contrast to the group of patients with chronic migraine (Fig. 3).



Note: - differences regarding simple migraines are significant (\*-  $P<0.05$ , \*\* -  $P<0.01$ , \*\*\* -  $P<0.001$ )

**Fig. 3. Analysis of the results of the ID-migraine questionnaire.**

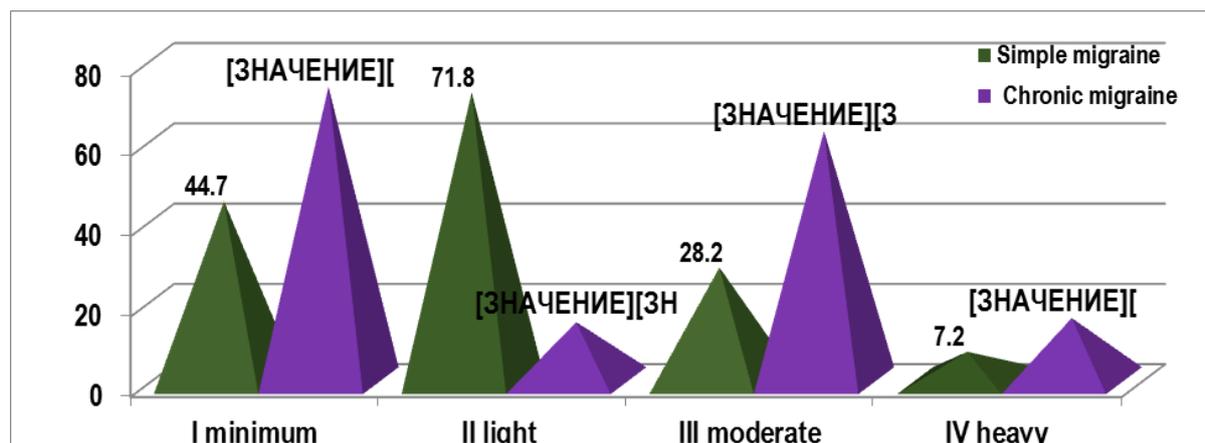
The combination of photo-and phonophobia prevailed in chronic migraines, as opposed to the simple form ( $P<0.05$ ). Phonophobia was the predominant symptom of chronic migraine, in contrast to photophobia ( $P<0.05$ ), which was apparently associated with the excitatory action of nociceptors, causing cortical depression. As can be seen, the ID-migraine questionnaire was an important diagnostic marker for patients suffering from chronic migraine and served for differential diagnosis of the nature of migraine headaches in chronic cephalgia and uncomplicated forms of migraine.

As the study shows, the ID-migraine questionnaire was a companion for patients, and these signs became the primary diagnostic marker for the differential diagnosis of chronic migraine from other types of headaches, the criteria of which were nausea, vomiting, phonophobia, photophobia and decreased performance.

The impact of migraines on overall health was assessed using the MIDAS scale, which allowed us to study the loss of performance due to GB in three main areas of life: study/work, work at home and family, sports/social activities. At the same time, we evaluated the completely "lost" days, as well as the number of days with a decrease in activity (by 50%), by daily recording them in the "Migraine" diary by the sum of answers to all five questions for 3 months. The assessment of migraine severity was performed by dividing the examined patients with migraine into 4 groups, where group I corresponded to a minimal decrease or absence of a decrease in performance and I degree of migraine severity, and group IV characterized a severe degree of migraine with complete loss of performance. The intensity of GB for qualitative and quantitative signs was characterized by testing patients with a one-dimensional scale of pain intensity –NRS, VRS and VAS, comparing them with the facial pain scale (Fig. 4).

Moderate II (8.8 points) and severe IV (23.6 points) were observed 1.5-2 times more often than mild I (4.2 points) ( $P<0.05$ ), while the most common (8.5 times) were patients with severe III (18.8 points) migraines with complete loss of performance during migraine paroxysms ( $P<0.001$ ). In patients with a simple form of migraine, moderate II degree of severity of the disease prevailed 5 times compared to chronic migraine.

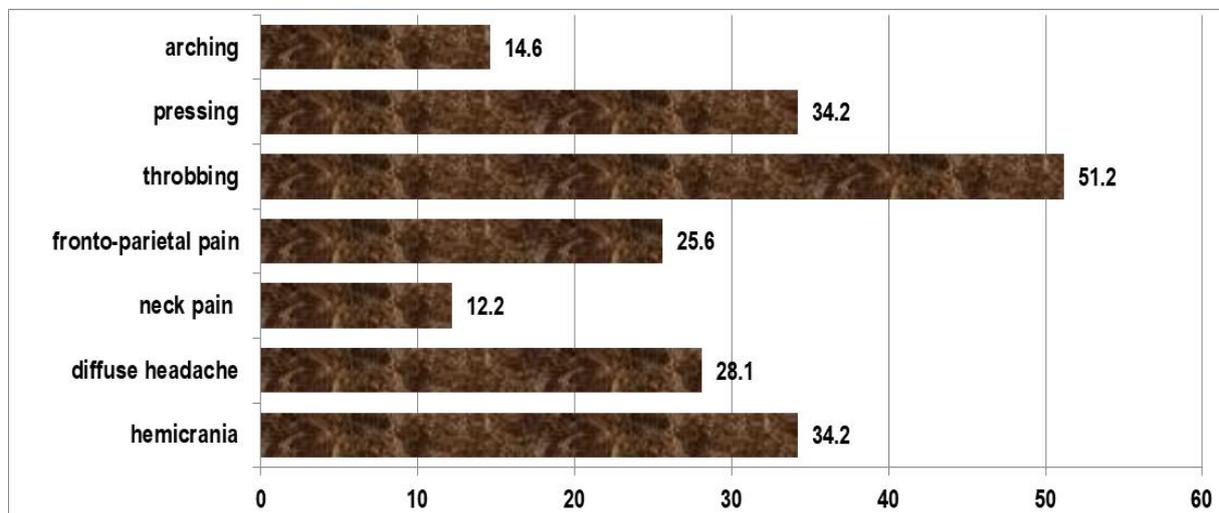
Along with qualitative and quantitative assessment of headache, we analyzed its nature and localization [Sanoeva M. Zh. et al, 2019].



Note: - differences regarding simple migraines are significant (\*-  $P<0.05$ , \*\* -  $P<0.01$ , \*\*\* -  $P<0.001$ )

**Fig. 4 Clinical severity on the MIDAS scale.**

The typical localization of hemicrania did not differ statistically from pain with diffuse distribution, but the frontal-parietal localization prevailed by 25% ( $P<0.05$ ). By nature, pulsating GB prevailed by 33%, with a pressure headache ( $P<0.05$ ), by 71.5%, and with a bursting GB ( $P<0.001$ ) (Fig. 5).



**Fig. 5** the Nature and localization of headaches in chronic migraine.

As can be seen, the MIDAS scale was a sensitive and feasible method for timely identification of severity of condition, assessing the health of patients, dependent on the intensity and duration of migraine attacks [Sanoeva M. J. et al, 2019].

In order to assess the functional state of the bioelectric potentials of the central nervous system, the total bioelectric activity of the brain was studied. The EEG of an adult is individual, it reflects to a certain extent his personal characteristics and pathological conditions of both cerebral and somatic genesis. The results of EEG study with an assessment of the functional activity of the surface layers and distant influences of the deep structures of the brain were studied.

In chronic migraine, there was a decrease in the amplitude of the alpha rhythm, the predominance of slow waves over fast ones, and the appearance of single pathological waves without zonal differences. Paroxysmal activity in the background curve was recorded regardless of the presence of migraine attacks, while patients with "Migraine with aura" were 1.7 times less than "Migraine without aura" ( $P<0.05$ ), accounting for 8 (11.9%) and 17 (20.7%) of the subjects, respectively. The rhythmic photostimulation test showed the appearance of photoparoxysmal activity in 12 (14.6%) patients, which was 2.0 times less than

in the background curve ( $P < 0.01$ ). the same difference was observed in the hyperventilation test ( $P < 0.05$ ), which represented bilateral flashes with high-amplitude alpha, theta, and delta waves, with their predominant localization in the temporal, Antero-frontal and parietal regions. On the basis of spectral analysis in chronic migraine was observed proportional of fast and slow waves activity, mainly in bilateral localization. When comparing groups of patients with simple migraine, there was a significant increase in alpha activity in the central-parietal region of the left hemisphere with spread to the anterior parts of both hemispheres, in chronic migraine, theta activity increased in the central-parietal and occipital regions of the hemispheres, while beta activity was significantly increased than the other waves. The appearance of paroxysmal activity in simple migraines was 2.8 times less than in chronic migraines ( $P < 0.01$ ).

Consequently, mild regulatory changes in bioelectric activity were typical in patients with simple migraine, while a significantly disorganized, desynchronous type of EEG with the appearance of pathological waves was observed in chronic migraine. Similar features for these groups were polymorphic activity and a sign of "perverse zonal diversity", which indicated a decrease in the functional activity of neurons in a state of adaptive tension, due to reactive angiostonia and cortical stimulation by the nociceptive action of migraine paroxysms.

Based on the identified changes in brain biopotentials, we developed a predictive system that allowed us to identify individuals with an increased risk of vascular deficit (HRVD) (acute or chronic) based on the Framingham scale [Sorokina N. D., 2018; Sanoeva M. J., 2020], and to determine the criteria (predictors) of the pathological pattern in patients with chronic migraine. In the presence of an organized type of EEG (I-type), the risk of developing brain ischemia is  $HRVD=0$  (the criterion is a pronounced  $\alpha$ -rhythm organized by the bilateral regions, with a frequency of 8-13 Hz); in the presence of light changes-hypersynchronous type II-there is a low risk of vascular deficiency, the risk level  $HRVD=1.0$  (the criterion is the appearance in one or more areas of the brain of slow theta (4-8 Hz) and delta activity (0.3-4 Hz) with an amplitude of up to 30 mV, fast asynchronous oscillations against a fairly regular alpha rhythm); the average risk level  $HRVD=3.0$  is observed with moderate changes in bioelectric activity, desynchronous type III EEG (the criterion is diffusely expressed disorganization of all rhythms, the appearance of a non-dominant curve, at a low amplitude level no higher than 30-35 mV, alpha activity is irregular, beta activity is unstable, and the

characteristic appearance of low-amplitude slow activity). Pronounced disorganized type IV EEG, refers to a high risk of brain ischemia HRVD=5.0 (the criterion is the absence of zonal differences in bioelectric rhythms in the presence of gross irregular pathological components:  $\beta$ -rhythm-13-25 Hz,  $\beta$ -rhythm-4-8 Hz;). The presence of a gross disorganized - V type refers to a very high risk of developing brain ischemia HRVD=5.0+ (the criterion is the appearance of gross irregular pathological components with a clear zoning of the lesion: the presence of theta (4-8 Hz) and Delta (0.3 - 4 Hz) rhythms). 29.9% were at high risk (HRVD=5.0) and 23.9% of patients with chronic migraines were at very high risk (HRVD=5.0+). 40.5% of patients with simple migraine were assigned to a low risk group (HRVD=1.0) for developing vascular deficits (table 1).

**Table 1: Prognostic system of acute cerebrovascular treatment for migraines.**

EEG types	Group			
	Simple migraine (n=42)		Chronic migraine (n=67)	
	abs	%	abs	%
I	17	40,5	6	9,0**
II	18	40,5	11	16,4**
III	4	9,5	14	20,9**
IV	2	4,8	20	29,9***
V	1	2,4	16	23,9***

Note: - differences regarding simple migraines are significant (\*-  $P<0.05$ , \*\* -  $P<0.01$ , \*\*\* -  $P<0.001$ )

Studies show that migraine attacks, depending on the clinical severity and course, duration and frequency of attacks of the disease can become a risk of developing acute and chronic blood flow disorders in the brain.

Dopplerographic indicators for chronic migraine showed a 15-18% decrease in blood flow in the extra cranial parts of the common carotid artery (CCA) compared to the simple form of migraine, without significant asymmetry of the sides. When analyzing data in a statistical decrease of the index of Pourcelot (30%), Stewart (by 40-45%) and Gosling (15-20%) in the studied vessels confirmed the deterioration in peripheral resistance, tone and viscoelasticity, increased hypo perfusion of the brain, and this reduction held steady in the interictal period ( $p<0.001$ ), meanwhile, the linear velocity of blood flow (LVB) reduction was mainly isolated reduction in  $V_{min}$ . Long-term headaches were accompanied by a hemodynamically significant decrease in LVB for the main trunks (CCA, ICA (internal carotid artery)) (up to 30%), but

such changes did not correlate with EEG results, which was apparently associated with compensatory brain perfusion by collaterals. In 16 (34.8%) patients, there was a decrease in blood flow for middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA), mainly due to  $V_{max}$ . In 15 (32.6%) there was an increase in  $V_{min}$ , with the relative preservation of  $V_{max}$  for ACA and PCA, of which 10 (21.7%) showed an increase in both  $V_{max}$  and  $V_{min}$ , 5 (10.9%) had an isolated increase in  $V_{max}$ , while in all cases peripheral circulatory resistance and vascular tonic properties were low ( $<0.57$ ), which confirmed the prevalence of vascular dystonia of the hypotonic type.

Signs of vertebrobasilar insufficiency were observed in 4 (8.7%) patients, which correlated with the basilar type of chronic migraine, venous dyscirculation mainly along the main artery (a.basilaris) was detected in 28 (60.9%) of the examined patients, and a decrease in blood flow along the anterior cerebellar artery was observed in 2 (4.35%) patients.

Vascular dystonia by hypotonic type correlated with a state of lethargy, rapid fatigue, drowsiness and a sharp decrease in performance in the post-seizure period.

The systolic and diastolic components of the blood flow rate in the CCA were inferior to 28% in chronic migraine, compared to the simple form of migraine. Also, the relatively low indicator of the average blood flow rate ( $V_{med}$ ) in the CCA in 29 (35.4%) patients with chronic migraine, while in the simple form of migraine, it did not change statistically in relation to the physiological norm ( $p<0.01$ ). The decrease in LVB was accompanied by a significant decrease in the peripheral resistance index of Purcelott ( $R_i$ ) to 21%, while the index of spectral expansion increased by 1.4 times, with the appearance of moderate blood flow turbulence. There was a simultaneous increase in the tone of the external carotid artery (ECA) ( $N=0.68-0.74$ ) – due to an isolated decrease in  $V_{min}$  in 12 (14.6%) patients due to a decrease in  $V_{max}$  and  $V_{min}$ . Statistically significant changes in blood flow in the extracranial parts of the vertebral artery (VA) were not observed.

The obtained results predetermined the study of autoregulatory abilities of brain vessels, which became the subject of predicting acute and chronic brain ischemias in migraines. The Overshoot coefficient (CO) was determined by pressing the CCA and registering blood flow in the middle cerebral artery (MCA) of the ipsilateral side, the normal value of which was  $N=1.23-1.54$  (table. 2).

**Table 2: Comparative analysis of the Overshoot coefficient.**

Group		V1 mm / sec	V2 mm / sec	Reduced blood flow %	V3 mm / sec	Increased blood flow %	OC
Simple migraine	Dex	84,5	53,6	36,6	106,6	49,7	1,26
	Sin	91,1	51,1	43,9	112,6	54,1	1,24
Chronic migraine	Dex	76,2*	55,6	27,0*	74,8*	25,7*	0,98**
	Sin	79,2*	57,4*	27,5*	78,6*	27,0*	0,99**

Note: - differences regarding simple migraines are significant (\*-  $P < 0.05$ , \*\* -  $P < 0.01$ , \*\*\* -  $P < 0.001$ )

As can be seen from table. 2 in chronic migraine after CCA compression, the blood flow rate in the ipsilateral MCA decreased by 1.4 times (25.0-28%), significantly differing from the comparison group (35-45%) ( $P < 0.05$ ), after stopping pressure, the blood flow increased by only 25-30%, statistically inferior to the simple form (50-55%), which showed a decrease in the reactivity of the cerebral arteries due to their hypotension. OC had a significant difference compared to the group of patients with simple migraine, yielding 20-22% in chronic migraine ( $p < 0.05$ ).

Thus, the observed signs – the decrease in the indices of resistivity of Pourcelot ( $R_i$ )  $< 0,57$  ( $N = 0,57-0,67$ ), pulsation of Gosling ( $P_i$ ) to 50%, making  $< 1,05$  ( $N = 1,05-1,17$ ), determining the tone, reactive abilities and resistance (peripheral and circulatory) of the vascular wall and decrease of the coefficient Overshoot 20-30%, amounting  $CO < 1,23$  ( $N = 1,23-1,54$ ) that defines the reserve capacity of the brain and the state of autoregulation of cerebral vessels, and the presence of venous discirculation at the same time, prove the reduction of adaptive-compensatory mechanisms thus, being signs of predicting acute and chronic brain ischemia, referred to as cerebrovascular complications, which have a direct correlation with bioelectric, clinical and neurological dysfunctions.

## CONCLUSIONS

1. Chronic migraine by its clinical course - prolonged migraine paroxysms, intense headaches, decreased performance. The severity of the patient's condition, Daily work activity forms a psychopathological state and reduces the quality of life of the patient.
2. Neurophysiological parameters of EEG can be objective indicators of the development of acute and chronic vascular complications in migraine, and our results prove the prevalence of organized EEG type in simple migraine and disorganized type in chronic migraine,

determining organic brain damage, which can be used to control and select differentiated adequate therapy for various variants of the clinical course of migraine.

3. Migraine paroxysms are the background for impaired quality abilities of cerebral vessels, and the frequency and duration of attacks change the normal physiology of blood supply to the brain, being a predictor of acute and chronic brain ischemia, referred as cerebrovascular complications.

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