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REACTIVITY OF BRAIN BLOOD FLOW IN PATIENTS WITH VARIOUS TYPES OF HEADACHE

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Abstract

The clinical characteristics and pathogenetic nature of the development of the main and most common forms of headache are described: migraine (M), tension headache (TTH), cervicogenic headache (CH). Moreover, the authors point to the need to study arterial and venous cerebral blood flow for a more complete understanding of the pathogenetic mechanisms of development of cephalalgia, with the obligatory study of cerebral autoregulation including myogenic, humoral-metabolic and neurogenic circuits.

The aim of the study was to assess the state of hemodynamics and cerebrovascular reactivity in patients with various types of headache.

458 young patients with M - 124 patients, TTH - 188 patients, and CH - 146 patients were examined. The control consisted of 45 clinically healthy volunteers of both sexes. Using transcranial dopplerography, the linear blood flow velocity of the cerebral arteries was studied. Cerebrovascular reactivity was evaluated using functional loads: hypercapnic, hyperventilation, ortho- and anti-orthostatic, functional nitroglycerin and metabolic tests.

The results obtained during the study indicate that: in patients with M, autoregulatory disturbances along the metabolic contour predominate - a hyperdilatory reaction in M without an aura and a hyperconstrictive reaction in M with an aura. Functional nitroglycerin test hyperreactivity is a specific pattern in both clinical groups of patients with M. Hyperreactivity to a functional metabolic test is similar in groups of patients with TTH and CH.

The leading metabolic pathway reactivity patterns in patients with GBI were: tension of the vasodilator mechanism in episodic TTH and depletion of the vasoconstrictor mechanism in chronic TTH. Hyperresponsiveness to orthostatic load associated with the neurogenic regulatory circuit was observed in all clinical groups of patients with headache and was probably associated with maladaptation and dysfunctional changes in autonomic structures.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: *migraine, tension type headache, cervicogenic headache, cerebral hemodynamics, cerebrovascular reactivity, transcranial doppler*

Introduction

Headache is now one of the most common complaints in various pathological conditions. The modern classification of headaches (ICHD-3, 2018) highlights primary headaches that make up the essence of the disease itself (migraine, tension headaches, cluster headaches) and secondary headaches, in which the headache is a symptom of some pathological process [8]. Migraine is one of the most widespread forms of headache; it can reach 22% in women and 16% in men [11].

In accordance with the classification, migraines can be split into two main forms:

1. Migraine without aura - a clinical syndrome characterized by headache attacks with specific accompanying symptoms.

2. Migraine with aura is characterized by local neurological symptoms that precede the headache or accompany it. A signal symptom of the headache may occur several hours or days before an attack. In some cases, symptoms may persist after the attack (post-attack phase) [5].

Migrainous pain consists of three components:

1. Vasodilation of large cerebral arteries and vessels of the dura mater and

2. Perivascular neurogenic inflammation.

3. Activation of the spinal tract of the trigeminal nerve and its central paths [5, 6].

The migrainous attack begins with the so-called spreading cortical depression of Leo. The pathogenetic factor of the attack is triggered by changes in metabolism and function of the cortex [7]. Changes in cerebral blood flow during the migrainous attack are similar to the stages of spreading depression. The rate of oligemia is approximately equal to the rate of pervasive depression during the migrainous attack [2, 14]. Various external factors can trigger the development of the migrainous attack: mental, nervous or physical overstrain, stress, weather factor, sleep disturbance, intake of certain foods or alcohol, the use of hormonal contraceptives. Transcranial Doppler (TCD) usage for cerebrovascular reactivity (CVR) evaluation is of informative character in patients with migraine. Studies have shown hyperreactive response of cerebral arteries to respiratory retention, hyperventilation, visual stimulation, and use of nitroglycerin [19-21]. This demonstrates that cerebrovascular reactivity may be a marker of migraine severity. The available publications do not contain any data on results of combined study of cerebral hemodynamics and cerebrovascular reactivity using the TCD method in patients with various types of migraine paroxysms.

Tension type headache (TTH) is the most common type of primary headache,the prevalence of which, according to various sources, varies from 30 to 80%. TTH diagnostic criteria are bilateral localization, compressive or constricting nature of the pain, mild or moderate pain intensity, absence of headache exacerbation with normal physical activity [9, 12, 22]. Long-term pain stimulation caused by intracerebral vessels (mainly venous) can provoke tension of the trapezius and sternocleidomastoid muscles controlled by motor neurons of the anterior horns of the C1-C3 segments of the spinal cord and the nucleus of the accessory nerve, and cause the development of TTH by switching from the nucleus of the spinal path of the trigeminal nerve to the above nuclei [9].

The sources of the headache are predominantly basilar arteries, extracranial arteries, walls of large venous sinuses, cranial base. Sensitization of the central nervous system to prolonged pain impulses and shortage of antinociceptive system are important pathogenetic factors in the development of chronic TTH [9]. Long-term irritation of the structures innervated by the sensitive branches of the trigeminal nerve, as well as the first and second roots of the spinal cord, lead to reflex tension of the pericranial muscles [12, 16]. In return, a prolonged nociceptive impulse from tense pericranial muscles leads to the sensitization of the central nervous system, which contributes to the headache chronicity [12, 16].

The cervicogenic headache (CH) or pain caused by the pathology of the cervical spine, one-sided as a rule, of cervical-occipital localization, is clearly associated with the movements in the cervical spine (turns, tilts of the head, uncomfortable posture, etc.) [18]. Most often, CH occurs with pathological changes in the cervical spine of degenerative-dystrophic nature (dystrophic processes in discs, instability of the cervical spine, uncovertebral arthrosis, etc.), leading to compression or irritation of sensitive nerve roots, sympathetic nerves with

subsequent reflex tension of the neck muscles and occipital region, which may be a substrate of pain [18, 23]. The pathophysiological basis of CH is the close connections of the first three cervical sensitive roots with the trigeminal nerve, forming the trigemino-cervical system [3]. In CH, it is assumed that not only peripheral, but also central mechanisms are involved, namely, altered reactivity of the structures of the limbic-reticular complex and dysfunction of the antinociceptive control. Pain in the cervical spine is caused by the excitation of pain receptors of the following structures: apophysical (facet) joints, fibrous ring, ligaments, periosteum, muscles and tendons; roots and nerve trunks; vertebral arteries [3]. The most common place of CH localization is the occipital region. Pain radiation more often occurs in the temporal, parietal and/or frontal areas and the homolateral orbit. The pain is often defined as a dull pain of moderate intensity. The pain is paroxysmal, lasts from several hours to several days and varies in intensity [3, 18]. The method of TCD makes possible not only the spatial localization of the pathological process in the vessels of the cervical spine, but also gaining an accurate information on the indicators of vertebral hemodynamics [4, 16].

Cerebrovascular reactivity reflects the state of adaptation mechanisms of the system of cerebral blood flow and the ability of cerebral vessels to change the blood flow in response to the changes of the vascular system conditions. The use of functional loads objectifies the activity of the regulatory mechanisms controlling cerebral blood circulation [13]. The TCD method allows you to get an idea of the system of arterial and venous cerebral blood flow, as well as cerebral autoregulation, which is directly related to integrative regulatory mechanisms. TCD helps to study the mechanisms of blood supply regulation to the brain, including myogenic, humoral-metabolic, and neurogenic contours [9, 15, 20]. In this regard, the question of the role of vascular factors is relevant for studying the pathogenetic mechanisms of headache development. [1, 10, 17]. The use of this method in patients with various types of headache is promising in further study of the pathogenesis of these nosological forms.

The aim of the study was to assess the state of cerebral hemodynamics and cerebrovascular reactivity in patients with various types of headache.

Methods

458 young patients (16 - 44 years old, men - 203, women - 255) with various types of headache were examined; including migraine (M) - 124 patients (group 1 (migraine without aura) - 63 patients, group 2 (migraine with aura) - 61 patient), tension type headache - 188 patients (group 1 (infrequent episodic TTH (IETTH) - 68 patients, group 2 (frequent episodic TTH (FETTH) - 64 patients), group 3 (chronic TTH (CTTH) - 54 patients); cervicogenic headache - 146 patients (group 1 - cervicocranialgia (CCA) - 82 patients; group 2 - posterior cervical sympathetic Barré–Liéou syndrome (BLS) - 64 patients).

The diagnosis was made in accordance with the diagnosis criteria of the International Classification of Headache of the 3rd revision [5]. Characteristics of headache were assessed using a questionnaire that allows to identify the type of headache that a patient possesses, assess its main qualitative and quantitative characteristics, provoking factors, accompanying symptoms, methods of pain relief, the presence of an abusus factor.

The state of blood flow in cerebral arteries and indicators of CVR were studied using Ultima PA ultrasound device (RADMIR, Ukraine) and Angiodin transcranial Doppler apparatus (BIOSS, Russia). We have studied the indicators of linear blood flow velocity (BFV) in middle cerebral (MCA), anterior cerebral (ACA), posterior cerebral (PCA) arteries, internal carotid arteries (ICA) siphons, vertebral (VA) and basilar (BA) arteries.The state of cerebrovascular reactivity was assessed using the following functional loads: hypercapnic reactivity (reactivity coefficient to hypercapnic (CrCO2)), and hyperventilation reactivity (CrO2) test, orthostatic (CrOL) and antiorthostatic (CrAOL) loads, functional nitroglycerin (CrFNT) and functional metabolic (CrFMT) tests.

The control group (CG) consisted of 45 patients of the corresponding gender and age. Statistical analysis and processing of the material was carried out using Statistica 6.0 software package. Differences with the CG indices were recognized as statistically significant at $p < 0.05$.

Results

The ICA, ACA, VA, CA blood flow indices in patients with migraine generally corresponded to the CG indices. In this group of patients, LBV was significantly enhanced compared with CG in MCA (84.4 ± 9.1 cm/s; CG - 62.6 ± 8.3 cm/s, p <0.05) and in PCA (56.7 ± 6.2 cm/s; CG - 36.4 ± 5.1 cm/s, p <0.05). In a significant number of patients with M (46.8%), LBV asymmetry (20-30 %) was revealed in the main intracranial arteries, mainly in MCA (29.8%) and PCA (19.3%). Patients with TTH did not show significant differences in speed indices compared with CG. Changes in hemodynamics were detected in 18.1% of patients and manifested themselves as insignificant increase in LBV (mainly in MCA) and slight asymmetry of LBV in the main intracranial arteries. LBV asymmetry (20- 25%) was detected mainly in MCA and showed the presence of cerebral angiodystonia.

The vast majority (75.0%) of patients with CH showed the presence of vasospastic reactions in vertebro-basilar vessels, usually in one VA and BA (34.4%) or in one VA (20.4%), VA and BA - 15 patients (16.1%), vasospasm in both VA - 27 patients (29.0%). Velocity indicators in this group were significantly enhanced in VA (49.3 ± 5.6 cm/s) and BA (51.4 ± 4.9 cm/s) compared with CG (36.8 ± 4.7 and 39.6 ± 5.3 cm/s, respectively, p <0.05). The asymmetry of VA blood flow (25-30%) was observed in 32.2% of patients with CH and reflected the presence of the initial vascular discirculation in the vertebrobasilar basin.

LBV indices in cerebral arteries in patients with various types of headache are presented in Fig.1.

CVR indices in the control group subjects were: CrCO2 - 1.28 ± 0.04; CrO2 - 0.36 ± 0.05; CrOL - 0.13 ± 0.03 CrAOL 1.15 ± 0.04. CrFMT 1.18 ± 0.02, CrFNT - 0.16 ± 0.04. The patients with migraine showed the predominance of values of CrCO2, CrO2 and CrOL relative to CG. There was also an intergroup difference in CVR indices in this category of patients.

The patients of the 1st group showed hyperreactivity to CO2, the patients of the 2nd group - pronounced hyperreactivity to O2, which indicate the vasoconstrictive nature of vascular reactions. Also, in the patients with migraine there was a significant increase in CrFNT, more pronounced in the subjects of the 2nd clinical group (1.26 ± 0.04; p <0.05). An increased response to orthostatic loading in the patients with migraine indicates a dysfunction of the neurogenic regulatory link. The response to FMT and AOL as a whole did not differ from normative indices (Fig. 2).

The patients with TTH showed an increase in CrCO2 indices, correlating with an increase in the frequency of headaches (1.37 ± 0.04 in the group with IETTH, 1.43 ± 0.05 (p<0.05) in the group with FETTH and 1.39 ± 0.07 in the group with CTTH, 1.28 ± 0.05 in the CG). These changes indicated the tension of the vasodilator regulation mechanism, which manifests itself already in the early stages of TTH. A hyporeactive response to the O2 load was observed in the patients with FETTH (0.31 ± 0.04) and CTTH (0.30 ± 0.05 (p <0.05), compared with the CG patients (0.36 ± 0, 05).

A decrease in O2 reactivity is usually associated with the depletion of the vasoconstriction reserve and manifests itself in the process of headache chronicity. In the patients with IETTH, the regulation of vasoconstriction, reflected in CrO2 indices, was preserved. The patients with FETTH and CTH showed mild hyperreactivity to OL (0.18 ± 0.04 and 0.19 ± 0.03, respectively, CG - 0.13 ± 0.02).

CrFMT indices were significantly increased in all clinical groups. In the patients with IETTH, the values of this coefficient were 1.24 ± 0.03 (p <0.05), in the patients with FETTH - 1.25 ± 0.02 (p <0.05), in the patients with CTTH – 1.27 ± 0.03 (p <0.05). In the study of the reactivity to FNT and AOL, there were no significant differences from the CG indices in the patients with TTH; only in the patients with FETTH, the CrFNT was slightly increased.

CVR indices in the patients with TTH are presented in Fig.3.

It can be assumed that the humoral-metabolic contour of cerebrovascular reactivity plays a leading role in the pathogenesis of autoregulatory disorders in TTH. The analysis of autoregulatory indices in response to respiratory loads allows us to identify the leading patterns of reactivity in various TTH variants - the tension of the vasodilator mechanism in ETTH and the depletion of the vasoconstrictor mechanism in CTTH. The interest in the neurogenic regulatory mechanism, manifesting by the presence of hyperreactivity to OL, proves the multifactorial nature of changes in TTH associated with

maladaptation and dysfunctional changes in vegetative structures.

These changes, apparently, are associated with the tension of vasodilatory mechanisms, as well as with the depletion of the vasoconstriction reserve, which is manifested mostly in the process of headache chronicity. In the analysis of the reactivity of indices in TTH the attention is caught by similarities of basic reactivity patterns with those of the patients with TTH, which is an indirect confirmation of the hemodynamic significance of the mechanism of muscle dysfunction in the pathogenesis of both nosological forms.

In the group of patients with CH a significant hyperreactivity to FMT was noted (1.28 ± 0.03 in the group with the CCA and 1.29 ± 0.04 in BLS group; CG - 1.18 ± 0.02, p <0.05). Similarly to those hemodynamic patterns present in TTH, a hyperreactivity to OL (0.19 ± 0.04 in the group with a CCA; 0.21 ± 0.05 in the BLS group; 0.13 ± 0.03 in CG) and hyporeactivity to O2 (0.32 ± 0.04 in the group with CCA; 0.31 ± 0.05 in the group with BLS; 0.36 ± 0.05 in CG) were revealed. (Fig. 4).

According to modern concepts, the vascular mechanism is not the leading one in the structure of the CH formation. These studies indicate that the changes in the reactivity associated with the neurogenic regulatory factor, as well as with the vasoconstrictor link of the humoral-matebolic regulation contour, can affect cerebral hemodynamics in the patients with vertebrogenic headache.

The results of the conducted studies suggest that the leading role in the pathogenesis of autoregulatory disorders of the patients with headache is played by the humoral-metabolic contour of regulation of cerebral blood flow. The evaluation of the regulatory response to respiratory load with the identification of leading reactivity patterns - hyperdilatation and hyperconstriction turned to be informative for the patients with migraine. In this group, hyperreactivity was observed to the samples with CO2, O2, and also for OL. The evaluation of the vasodilation function by the myogenic contour with the use of FNT was also informative in this group. The conduct of FMT, modeling the response of cerebral reactivity mechanisms to mechanical tension, was the most informative method for detecting autoregulatory disorders in clinical groups of the patients with TTH and CB. The studies showed the tension of this contour during FMT evaluation even in the patients with IETTH, who largely consider themselves healthy and rarely seek a specialized help for the cephalgic syndrome. Also, hyporeactivity to the O2 load, associated with depletion of the vasoconstriction reserve, was observed in both groups. In addition, in the group of patients with TTH, hyperreactivity to the CO2 load was detected. The evaluation of the regulatory response to respiratory loads makes it possible to identify the leading reactivity patterns in various types of TTH - the tension of the vasodilator mechanism in ETTH and the depletion of the vasoconstrictor mechanism in CTTH. Also, the patients with IETTH showed mild hyperreactivity to the CO2 load, which confirms the postulate of the tension of the humoral-metabolic contour and allows us to recommend the use of FMT and CO2 test in the patients with mild manifestations of cephalgic syndrome. The participation of the neurogenic regulatory mechanism, determined by hyperreactivity to OL in all clinical groups, proves the multifactorial nature of changes in the vascular autoregulation system in patients with various types of headache.

Conclusions

1. Autoregulatory disorders on the metabolic contour dominate in the patients with migraine: hyperdilatatory reaction in migraine without aura and hyperconstrictory reaction in migraine with aura.

2. Hyperreactivity to the functional nitroglycerin test is a specific pattern in both clinical groups of patients with migraine.

3. Hyperreactivity to the functional metabolic test is similar in the groups of patients with TTH and CH.

4. The leading reactivity patterns on metabolic contour in the patients with TTH were the tension of vasodilator mechanism in ETTH and the depletion of the vasoconstrictor mechanism at CTTH.

5. Hyperreactivity to orthostatic load associated with the neurogenic regulatory contour was observed in all clinical groups of patients with headache and was probably associated with maladaptation and dysfunctional changes in the vegetative structure.

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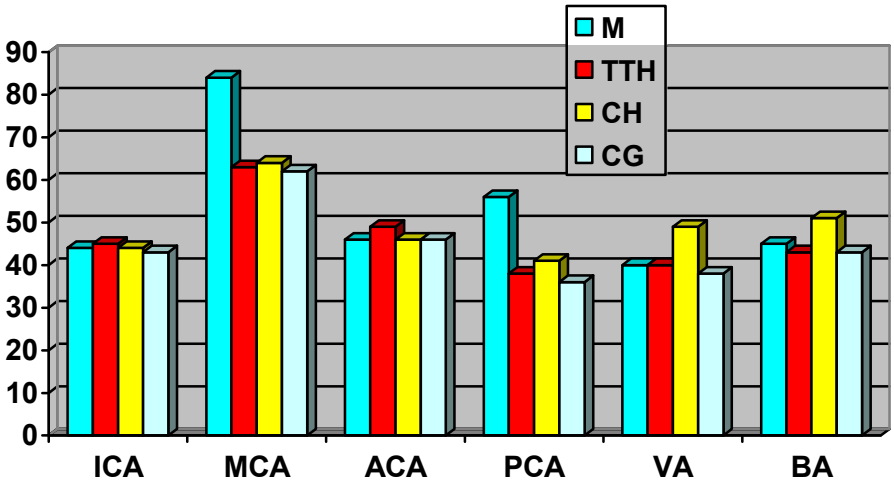

Fig.1. The LBV indicators in cerebral arteries in patients with various types of headache

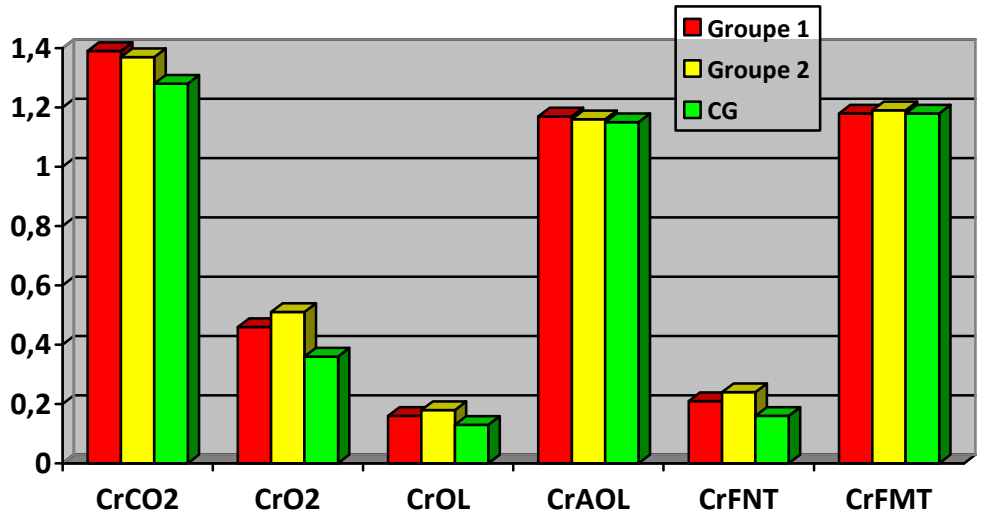

Fig.2. The CVR indicators in cerebral arteries in patients with migrane

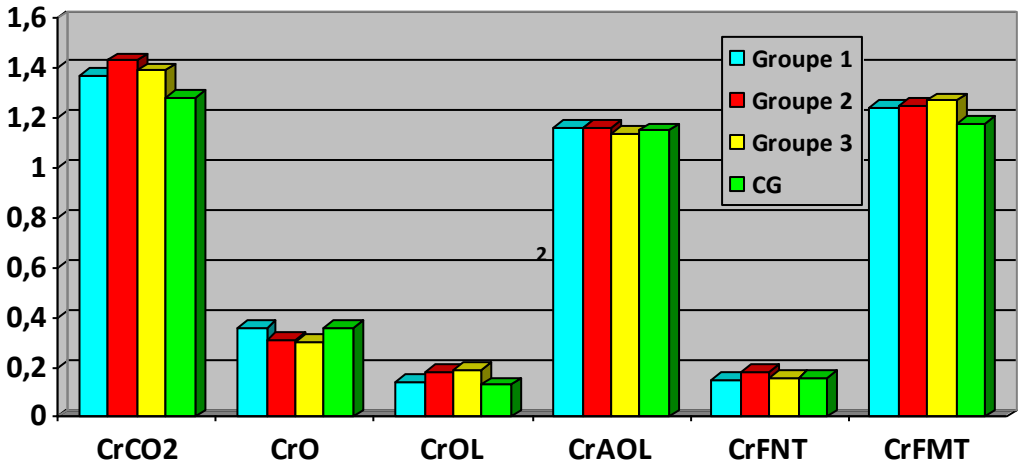

Fig.3. The CVR indicators in cerebral arteries in patients with TTH

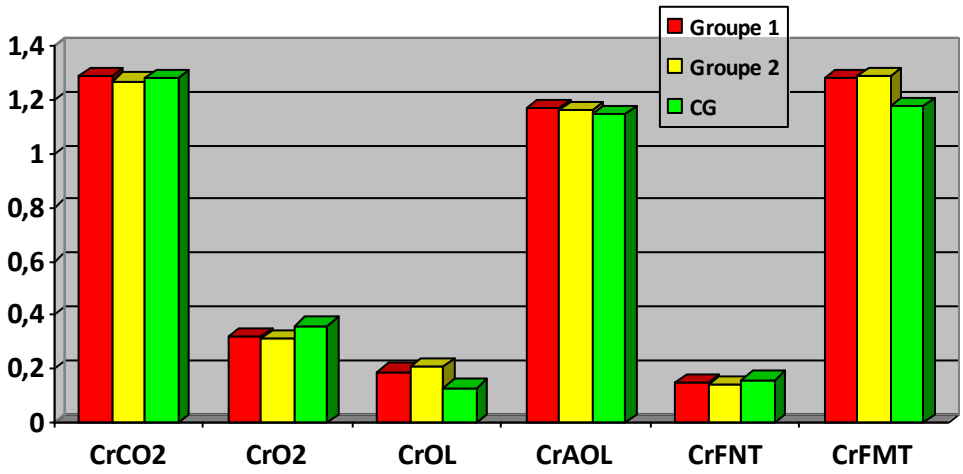

Fig.4. The CVR indicators in cerebral arteries in patients with CH