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The next issue is dedicated to the 90th birthday anniversary of F.A. Serbinenko

In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the Problems of Neurosurgery named after N.N. Burdenko was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.
Autoregulation of cerebral blood flow (ACBF) is a system of mechanisms for maintaining stable adequate perfusion of the brain despite changes in systemic arterial pressure. In recent years, new data on the numerous metabolic and systemic mechanisms of cerebral blood flow regulation have been obtained, but the role of neurogenic regulation has not yet been fully understood and, therefore, not considered in clinical practice.

**Aim.** The study aim was to assess the effect of anatomical injuries to deep brain structures on the extent and duration of ACBF abnormalities in a model of severe diffuse axonal injury (DAI).

**Results.** The study demonstrated that brain injury in the projection of a dopaminergic structure (substantia nigra) and a cholinergic structure (nucleus basalis of Meynert region) was more common in patients with impaired ACBF and was associated with a longer duration of the impairment.

**Conclusion.** The obtained data may indicate the presence of central (neurogenic) pathways of cerebral vessel tone regulation; traumatic injury of the pathways leads to a more severe and prolonged period of impaired ACBF. Probably, injury to these regulatory structures in some patients has an indirect effect on the course of intracranial hypertension. Further experimental and clinical studies in this direction are needed to elucidate all elements of neurogenic regulation of cerebral vessel tone and ACBF mechanisms.

**Keywords:** traumatic brain injury, diffuse axonal injury, autoregulation, cerebral blood flow, substantia nigra, Meynert nucleus.

Autoregulation of cerebral blood flow (ACBF) is a protective mechanism aimed at maintaining cerebral circulation in response to changes in cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR) [1]. The term was proposed by N. Lassen in 1959 [2]. In this case, CPP is the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP) and is inversely proportional to CVR. The CVR, in turn, is the total vascular resistance, including that of the pial arterioles and penetrating precapillary arterioles of the brain [3]. The rate of cerebral blood flow is directly proportional to CPP and inversely proportional to CVR.

There are several mechanisms involved in maintenance of the cerebral blood flow level (normal — 50 ml/100 g/min): 1) **metabolic** (blood pH, balance of CO₂/O₂, dissolved in blood, nitric oxide, adenosine, and substances produced by astrocytes and neurons) [4, 5]; 2) **myogenic** (the Ostroumov-Bayliss effect is a response of the arterial smooth muscles in the form of contraction or relaxation to an increase or decrease in arterial pressure (AP), respectively); 3) **peripheral (or systemic)** (activity of the sympathetic adrenal system and carotid glomeruli, temperature, endothelial factors); 4) **neurogenic** (the vasomotor center, centers regulating activity of the sympathetic system, and, probably, some other brain structures). Elements of the latter are the least studied.

All ACBF mechanisms provide maintenance of cerebral perfusion with fluctuations in AP within a range of 60—70 and 170—180 mm Hg. If AP occurs beyond this range, autoregulation failure develops, which is a condition when the cerebral blood flow passively depends on systemic AP, and ICP becomes directly dependent on arterial pressure. This condition may lead to both ischemia and “luxury perfusion” syndrome (reactive hyperemia) associated with a high risk of secondary ischemic or hemorrhagic complications.

ACBF is often impaired in the acute period of severe traumatic brain injury (sTBI) that is associated with unstable hemodynamics and leads to an unfavorable outcome. Assessment of the ACBF status currently serves as the main objective landmark for monitoring and correcting conservative treatment and deciding on neurological intervention in the acute period of sTBI [6]. For patients with autoregulation impaired due to sTBI, achieving the recommended CPP level (not less than 70 mm Hg) may be associated with cerebral hyperemia predisposing to intracranial hypertension, edema, and intracerebral hemorrhages [6]. Therefore, according to the latest recommendations, the required CPP limit for this group of patients is reduced to 60 mm Hg [7]. Recent studies [3] have shown that maintaining the CPP level below 50—60 mm Hg is associated with a large number of positive outcomes, while the CPP level more than 70—80 mm Hg more often leads to adverse outcomes in patients with impaired ACBF.

In classical studies by N. Lundberg [8], three types of spontaneous oscillations of ICP are distinguished: A-waves (plateau), B-, and C-waves. Subsequent studies demonstrated that plateau waves reflect cerebral vasodilation that leads to an increase in volumetric cerebral
blood flow and, consequently, an increase in ICP [9]. At present, an analysis of wave oscillations of arterial and intracranial pressure serves as one of the most reliable and safe methods for continuous evaluation of cerebral autoregulation in the acute period of sTBI — monitoring of the cerebrovascular pressure reactivity index (PRx). The PRx is the coefficient of correlation between slow wave oscillations of AP and ICP [10, 11]. Plateau waves of ICP in sTBI were demonstrated to be more often detected in the case of preserved autoregulation of cerebral vessels. At the time of plateau wave formation, maximum arteriole vasodilation develops, and autoregulation is lost, which is reflected by an increase in the PRx [12].

Earlier, experimental studies [13, 14] demonstrated that injury to certain brainstem and hypothalamic structures was accompanied by the development of cerebral edema. Electrostimulation of certain brainstem structures initiates processes leading to cerebral vasodilation and increased volumetric cerebral blood flow [15, 16]. The brainstem is supposed to be directly involved in the generation of waves typical of intracranial hypertension, but the anatomical pathways and mechanisms of this influence have not been sufficiently studied yet. Several experimental studies demonstrated the effect of stimulation of certain brainstem structures (including the locus coeruleus, reticular formation of the medulla oblongata, and hemispheric structures of the brain (in particular, the anterior cingulate gyrus and anterior hypothalamus) on changes in ICP [17]. Also, injury to the brainstem structures and frontal lobes was previously shown to change activity of the sympathetic nervous system that affects arterial tone [18].

A feature of DAI is predominant injury to the subcortical and brainstem structures involved in maintaining vital functions, including regulation of cerebral vascular tone and ACBF.

The purpose of this work is to identify anatomical injuries to the deep brain structures, which affect the severity and duration of ACBF disorders in the acute period of severe DAI.

Material and methods

The analysis included 37 patients with sTBI (a Glasgow coma scale score of 3 to 8) who were treated in the Critical Care Department of the Burdenko Neurosurgical Institute in the period between 2009 and 2014. Patients with clinical indications for monitoring of AP, ICP, and CPP and with MRI-detected signs of DAI matched the inclusion criteria. The monitoring data were saved, analyzed, and processed using the ICM Plus software. A total of 23 males and 12 females were included in the analysis; the patients’ mean age was 28±12.4 years. Seven patients of this group underwent decompressive craniectomy due to diffuse cerebral edema.

At the Critical and Intensive Care Department, patients underwent mechanical ventilation, sedation, and analgesia (propofol (1—3 mg/kg/h) or midazolam (10—30 µg/kg/h) and fentanyl (1 to 2 µg/kg/h)); PaCO2 was maintained at 35—45 mm Hg, and PaO2 was not less than 100 mm Hg. CPP was maintained above 60 mm Hg. If ICP was above 20 mm Hg, bolus administration of 15% mannitol (0.25—1 g/kg) or Hyperhaes at a dose of 2 to 3 mL/kg was used.

The Glasgow coma scale (GCS) [19, 20] was used to assess the depth of coma. TBI outcomes were assessed using the Glasgow outcome scale (GOS) [20, 21]. Injury to the brain in DAI was assessed according to a MRI-based classification [22]. The location and level of brain injury were assessed using a MRI-based classification proposed by N.E. Zakharova et al. [23].

In all patients, ICP was monitored according to the international recommendations and protocol of the Association of Neurosurgeons of the Russian Federation [7, 24]. ICP monitoring was performed using a Codman ICP Express Monitor and a Codman MicroSensor (Johnson & Johnson Professional, Inc., Raynham, USA). The ICP sensor was implanted into the white matter of the brain through a trephination hole in the Kocher’s point projection into the premotor area of the subdominant hemisphere. ACBF was assessed by monitoring the cerebrovascular pressure reactivity index, PRx [10]. The mean duration of PRx monitoring was 7 days. The ratio of the impaired autoregulation period to the total monitoring duration of this parameter was also evaluated.

AP was monitored by direct measurement through an arterial catheter placed in the radial or femoral artery or in the dorsalis pedis artery.

Based on the mean PRx index calculated for the entire period of ICP and CPP monitoring, two groups of patients were identified:

1st group — patients with preserved ACBF; PRx, [–1; 0];
2nd group — patients with partially or completely impaired ACBF; PRx, (0; 1].

The characteristics of patients in each group are presented in Table 1. Group 1 consisted of 19 patients. In 16 (84.2%) of them, the injury was caused by a traffic collision. In 15 (78.9%) patients, MRI revealed brainstem injury.

Group 2 involved 18 patients. In 15 of them, a traffic collision was the cause of injury. Seven patients underwent decompressive craniectomy due to diffuse cerebral edema. In 15 (83.3%) patients in this group, MRI revealed brainstem injury.

Neuroimaging techniques. MRI of the brain was performed on a GE 3T scanner in standard modes (T1, T2, FLAIR) and SWI/T2* GRE and DWI modes, which enabled assessment of both ischemic and small hemorrhagic foci. MRI data of each patient were used to assess injury to certain subcortical structures and brainstem areas, projections of the major brain neurotransmit-
ter systems (Fig. 1), as well as affected areas of the frontal lobes (medial, pole, and dorsolateral regions).

**Statistical techniques.** Data were processed using the Statistica 8.0 software package (StatSoft Inc, USA). In all cases, nonparametric tests were used for statistical evaluation. The Fisher’s test (F) was used to analyze qualitative indicators; the effect of anatomical factors on the risk of developing unstable hemodynamics was evaluated by calculating the odds ratio and sensitivity and specificity for each factor. The results were considered statistically significant at \( p < 0.05 \).

**Results**

An analysis of the MRI data demonstrated that all patients in the analyzed sample had signs of diffuse brain injury with involvement of hemispheric and brainstem (in 29 (78.4%) of 37 patients) structures. However, a small number of patients in groups with preserved and impaired autoregulation prevented establishing reliable differences in the outcomes of injury severity in GOS and GCS. There were no differences between groups in gender and age indicators. Also, there were no significant differences between compared groups in the location and depth of brain injuries assessed using classifications by R. Firsching et al. [22] and N.E. Zakharova et al. [23], (Table 1).

1. Occurrence of injury to the brainstem and subcortical structures in impaired ACBF

A statistical analysis of the occurrence rate of unilateral and bilateral injury to each brain structure was then performed in patients with impaired (group 2) and preserved (group 1) autoregulation (Table 2).

The statistical analysis of data showed that injury to the brainstem in patients with traumatic brain injury accompanied by ACBF disorders in the acute period of trauma occurred somewhat more frequently than in the group of patients with normal autoregulation. Among the studied brainstem structures, structural injury to the midbrain substantia nigra, a structure that is the source of dopaminergic projections for the neostriatum, cingulate cortex, olfactory nuclei, posterior hypothalamus, and amygdalas of the brain, occurred more often (\( p = 0.02 \)) in patients of the 2nd group. The odds ratio amounted to 5.333 (95% CI, 1.252; 29.346), the sensitivity was 62.5%, and the specificity was 76.2%. Also, more frequent injury to a cholinergic structure, the Meynert nucleus area, was revealed in patients with impaired autoregulation (\( p = 0.01 \)), with unilateral or bilateral injury to this brain region being highly specific (81%) for patients of this group. In addition, we evaluated the occurrence rate of combined injury to the substantia nigra and Meynert nucleus, which significantly prevailed in the impaired autoregulation group (\( p = 0.02 \)). The odds ratio amounted to 7.39 (95% CI, 1.043; 65.37), the sensitivity was 43.8%, and the specificity was 90.5%.

Thus, the analysis demonstrated that impaired autoregulation of cerebral blood flow in patients with brain DAI was often associated with the presence of primary injury to the substantia nigra, Meynert nucleus area, and their combination (Fig. 2).

**Table 1. Comparative analysis of groups with preserved and impaired ACBF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group with preserved autoregulation (n=19)</th>
<th>Group with partially or completely impaired autoregulation (n=18)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>27.7 (18; 40)</td>
<td>33.4 (20; 63)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>12/7</td>
<td>11/7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>GOS after 3 months</td>
<td>6 (3; 8)</td>
<td>5 (4; 7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MRI-based classification of sTBI according to R. Firsching (2001)</td>
<td>3 (1; 4)</td>
<td>3 (3; 4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MRI-based classification of brain injury according to N.E. Zakharova (2016)</td>
<td>2 (1; 3)</td>
<td>2 (1; 4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rate of brainstem injury (number of patients, %)</td>
<td>6 (3; 7)</td>
<td>5 (4; 7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rate of hemodynamic instability (number of patients, %)</td>
<td>15 (78.9)</td>
<td>14 (87.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Duration of hemodynamic instability, days</td>
<td>17 (80.9)</td>
<td>12 (75)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Maximum ICP, mm Hg</td>
<td>7.8 (0; 19)</td>
<td>5 (0; 15)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Intracranial hypertension duration, days</td>
<td>33.8 (14; 51)</td>
<td>26.3 (11; 45)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PRx</td>
<td>−0.1 (−0.2; −0.03)</td>
<td>0.14 (0.02; 0.33)</td>
<td>&lt;&lt;0.05</td>
</tr>
<tr>
<td>Duration of completely impaired autoregulation PRx&gt;0.2 (% of the monitoring duration)</td>
<td>15.7 (10; 21)</td>
<td>43.8 (27; 76)</td>
<td>&lt;&lt;0.05</td>
</tr>
</tbody>
</table>

Footnote. Abbreviations: GCS — Glasgow coma scale, GOS — Glasgow outcome scale, DAI — diffuse axonal injury, ICP — intracranial pressure, ICH — intracranial hypertension, PRx — cerebrovascular pressure reactivity index.
2. Occurrence of injury to the subcortical and brainstem structures during prolonged impaired autoregulation

To analyze the effect of injury to the subcortical and brainstem structures on the blood flow autoregulation parameter (PRx), patients were divided into three approximately equal groups, depending on the duration of impaired autoregulation (PRx>0.2) relative to the entire measurement time: 1) less than 20% of the time (n=17); 2) 20—34% of the time (n=10); 3) >35% of the time (n=10). The results of this analysis are presented in Table 3.

In patients with autoregulation impaired for more than 35% of the measurement time, brainstem injury was found to be somewhat more frequent. In this group of patients, injury to the substantia nigra was significantly more frequent (p=0.05). The odds ratio was 5.6 (95% CI, 0.785; 45.938), and the sensitivity and specificity were 70 and 70.6%, respectively. Also, injury to the Meynert nucleus area was more frequent in this group (p=0.04).
The odds ratio was 7.6 (95% CI, 1.006; 68.466), and the sensitivity and specificity were 70 and 76.5%, respectively.

According to the results of this analysis, significant differences in the rate of injury to the substantia nigra, Meynert nucleus area, and their combination remained between the extreme groups (impaired autoregulation duration of less than 20% and more than 35% of the measurement time). Therefore, primary injury to the brainstem in the substantia nigra and basal forebrain (Meynert nucleus) region contributes significantly to impairment of ACBF mechanisms.

**Discussion**

We proposed a hypothesis on the effect of certain neurotransmitter brain structures, as central components, on ACBF in severe brain trauma, which had not been previously described in the literature. Our findings with the DAI model may be explained using previously obtained data about other human brain diseases (mainly neurodegenerative) and experimental studies.

At present, many neurotransmitter systems are believed to be able to affect blood flow through receptors located on the capillaries or perivascular glia. These effects have been demonstrated, in particular for dopamine that has two types of receptors: D1- and D2-like receptors exhibiting vasorelaxing and vasoconstricting activity, respectively. In humans, dopamine causes constriction of large cerebral arteries and, thereby, increases the linear velocity of cerebral blood flow [26].

The substantia nigra functionally belongs to the extrapyramidal system because it participates in muscle tone regulation upon motor functioning. The least known and studied anatomical ways, through which the substantia nigra affects vegetative functions such as breathing, cardiac activity, and vascular tone. The substantia nigra contains two types of neurons; of these, some neurons use dopamine (pars compacta), while the others (pars reticulata) use glutamate. A number of experimental studies have shown that electrical stimulation of the substantia nigra pars compacta causes tachycardia and an increase in arterial pressure [25, 27—29]. Similar data indicate that dopaminergic neurons of the substantia nigra activate the central pathway of the cardiovascular depressor center, which is involved in inhibition of the sympathetic fibers that cause arterial contraction and an increase in the heart rate.

Substantia nigra dopaminergic neurons send projections to the basal forebrain system called the “extended amygdala”. The extended amygdala is closely related to the forebrain and brainstem structures involved in regulation of the cardiovascular system [29, 30]. Stimulation of the amygdala structures, as well as stimulation of the substantia nigra, leads to suppression of cardiovascular reactions [31, 32], which suggests that the structures constitute a single regulatory system. Previous studies demonstrated that the activity of substantia nigra dopaminergic neurons can be regulated by arterial baroreceptors [33, 34]. Denervation of the baroreceptors leads to a decrease in the production and release of dopamine into the striatum. These data indicate an important fact that dopaminergic neurons of the substantia nigra may be part of a long-loop central baroreceptor reflex pathway regulating AP [35].
There is evidence that cholinergic neurons also participate in the regulation of regional cerebral blood flow [36, 37], and this regulation mechanism does not depend on regional metabolism and systemic AP. Activation of cholinergic fibers of the Meynert nucleus and septal complex leads to the release of acetylcholine in the cortex and hippocampus, which causes an increase in cerebral blood flow in these structures. A diffuse increase in blood flow in the cortex during walking is associated with excitation of the vasodilative system of the basal Meynert nucleus [36]. Activation of cholinergic neurons in the basal forebrain may contribute to an increase in ICP and formation of plateau waves due to vasodilation [17].

In a number of neurodegenerative diseases of the brain (Parkinson’s disease, multisystem atrophy), autoregulation is also impaired, which is associated with autonomic dysfunction [38]. However, each component of the vegetative system has its own representation in the central nervous system, in particular in the brainstem. A clinical model for understanding the role of the substantia nigra in regulation of blood flow is Parkinson’s disease, a disorder characterized by a progressive loss of dopaminergic neurons of the substantia nigra. Experimental studies simulating this disease indicated a decrease in the sympathetic component in regulation of AP and heart rhythm upon degeneration of the substantia nigra [39].

Fig. 2. MRI scans of the brain in patients with severe TBI affecting the substantia nigra (a), Meynert nucleus area (b), and both the substantia nigra and Meynert nucleus area (c). Injuries are indicated by arrows.
Conclusion

Therefore, this study demonstrated that injury to the dopaminergic structure of the substantia nigra and the cholinergic structure of the Meynert nucleus area in DAI patients was associated with more pronounced and prolonged impairment of cerebral blood flow autoregulation. The obtained data indicate that humans have neurogenic mechanisms of cerebral vessel tone regulation, which contribute to a change in ICP. Traumatic injury to these regulatory components is associated with a more severe and prolonged period of impaired autoregulation of cerebral blood flow, which may require longer monitoring and correction of ICP.

Our findings demonstrate the presence of different brain injury patterns in patients with impaired and preserved mechanisms of cerebral autoregulation in similar severity and clinical form of TBI. Our findings, from the clinical side, indirectly confirm the results of previous experimental studies on the presence of direct neuronal mechanisms of vascular tone regulation. However, these data should be carefully interpreted because they are preliminary and just lift the veil a little on the complex mechanisms of cerebral blood flow regulation in acute brain pathology. Undoubtedly, further, more detailed research in this direction is required, in particular for identification of all components of the neuronal regulatory system.

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Authors declare no conflict of interest.

REFERENCES


Table 3. Rate of injury to brain structures in patients with a different duration of impaired autoregulation (as a percentage of the ICP measurement duration)

<table>
<thead>
<tr>
<th>Duration of impaired autoregulation</th>
<th>&lt;20% (n=17)</th>
<th>20—34% (n=10)</th>
<th>&gt;35% (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>4.5 (4.7)</td>
<td>5 (3.6-5.5)</td>
<td>6 (4.7-5.5)</td>
</tr>
<tr>
<td>GOS</td>
<td>3 (3.4)</td>
<td>2.5 (1.4)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Brainstem injury, %</td>
<td>13 (76.7)</td>
<td>8 (80)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>LC (locus coeruleus), %</td>
<td>4 (23.5)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Ventral tegmental area (VTA), %</td>
<td>4 (23.5)</td>
<td>2 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Substantia nigra (SN), %</td>
<td>5 (29.4)*</td>
<td>3 (30)</td>
<td>7 (70)*</td>
</tr>
<tr>
<td>Laterodorsal tegmental nucleus (LDT), %</td>
<td>2 (11.8)</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Pedunculopontine tegmental nucleus (PPT), %</td>
<td>4 (23.5)</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Meynert nucleus (MN), %</td>
<td>4 (23.5)*</td>
<td>1 (10)*</td>
<td>7 (70)**</td>
</tr>
<tr>
<td>Globus pallidus internus (GPi), %</td>
<td>6 (35.3)</td>
<td>2 (20)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Globus pallidus externus (GPe), %</td>
<td>9 (52.9)</td>
<td>3 (30)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Putamen (Put), %</td>
<td>8 (47.1)</td>
<td>4 (40)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Nucleus caudatus (NC), %</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Thalamus (Tha), %</td>
<td>5 (29.4)</td>
<td>5 (50)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Nucleus ruber (NR), %</td>
<td>5 (29.4)</td>
<td>2 (20)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Central tegmental area (CTA), %</td>
<td>10 (58.8)</td>
<td>4 (40)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Medio basal frontal lobes, %</td>
<td>6 (35.3)</td>
<td>3 (30)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Frontal lobe poles, %</td>
<td>8 (47.1)</td>
<td>4 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Lateral frontal lobes, %</td>
<td>2 (11.8)</td>
<td>1 (10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Combined injury to the Meynert nucleus and substantia nigra, %</td>
<td>2 (11.8)</td>
<td>1 (10)</td>
<td>6 (60)*</td>
</tr>
</tbody>
</table>

Footnote. * — differences between the 1st and 3rd groups; # — differences between the 2nd and 3rd groups.
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mias in Parkinson’s disease: cardiovascular changes and autonomic modu-
Received: 07.02.18
The 1960—1970s were marked by intensive research of cerebral circulation and autoregulation of cerebral blood flow (ACBF). Morphological studies revealed nerve fibers in the walls of the cerebral vessels, ranging from the circle of Willis and its branches to the smallest arterioles. Nerve cells, fibers, and receptors were found in connective tissue strings stabilizing arteries in the cerebrospinal fluid channels of the subarachnoid space. The main arteries are richly innervated, in particular an abundant nervous network is present in the internal carotid artery siphon region. Nervous regulation of cerebral circulation is doubtless. However, the mechanisms of this regulation remain unexplored. First of all, we do not know the nature of central mechanisms involved in regulation of the cerebral vessel lumen. Some researchers suggest that the function of this regulation center may be performed by neurons or their groups located in the cortex, near the effector arteries; other researchers search for this center in the reticular formation, roof nuclei, and hypothalamus.

The authors investigated ACBF in 37 patients with cerebral DAI by monitoring of the cerebrovascular pressure reactivity index. All patients were divided into two groups comparable in the other indicators: a group with preserved ACBF (19 patients) and a group with partially or completely impaired ACBF (18 patients). MRI revealed 15 patients with injury to the brainstem structures in each group. A statistical analysis using a modern software package revealed that brain injury in projections of a dopaminergic structure of the substantia nigra and a cholinergic structure of the substantia innominata of Meynert area was significantly more frequent in patients with impaired ACBF. The revealed pattern is not only of theoretical interest but also of great practical importance.

Injury to the substantia nigra and Meynert nucleus is known to be pathognomonic for Parkinson’s disease. Deterioration in condition of patients after surgical treatment complicated by pneumocephalus might be explained by ACBF disorders. Recent studies have confirmed changed autoregulation in idiopathic parkinsonism. However, this is not necessarily an ACBF disorder. Probably, the central mechanisms of ACBF are much more complex than just localization of them in the brain structures indicated by the authors.

The issue addressed in this article certainly requires further detailed research. The study findings deserve to be published.

A.L. Krivoshapkin (Moscow, Russia)
Extended Endoscopic Endonasal Posterior (Transclival) Approach to Tumors of the Clival Region and Ventral Posterior Cranial Fossa. Part 3. Analysis of Surgical Treatment Outcomes in 127 Patients

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Burdenko Neurosurgical Institute, 4-ya Tverskaya-Yamskaya Str., 16, Moscow, Russia, 125047

Until recently, tumors of the clival region and ventral posterior cranial fossa were considered hard-to-reach and often inoperable via standard transcranial approaches. The introduction of minimally invasive methods combined with the endoscopic technique into neurosurgical practice has enabled removal of hard-to-reach tumors, including midline tumors of the ventral posterior cranial fossa.

Objective — to improve and introduce the extended endoscopic endonasal posterior (transclival) approach into clinical practice and to analyze the results of its application in surgical treatment of midline skull base tumors extending into the ventral posterior cranial fossa.

Material and methods. During the period from 2008 to the present, we have operated 127 patients with various skull base tumors located in the clival region and ventral posterior cranial fossa (60 males and 67 females); the patients’ age was 3 to 74 years. The distribution of tumors by histology was as follows: 96 (75.6%) chordomas, 9 (7.1%) pituitary adenomas, 8 (6.3%) meningiomas, 3 (2.3%) cholesteatomas, 2 (1.6%) craniopharyngiomas, and 6 (4.7%) other tumors (giant cell tumor, glioma of the neurohypophysis, osteoma, plasmacytoma, carcinoid tumors, chondroma). The tumor size was as follows: 36 (28.35%) giant (more than 60 mm) tumors, 71 (55.9%) large (35—59 mm) tumors, 19 (14.96%) medium (21—35 mm) tumors, and 1 (0.79%) small (less than 20 mm) tumor. Intraoperative monitoring of the cranial nerves was performed (20 cranial nerves were identified) in 10 cases.

Results. The extent of chordoma resection was as follows: total removal — 63 (65.62%) cases, subtotal removal — 23 (23.96%) cases, and partial removal — 10 (10.42%) cases. Pituitary adenomas were resected totally in 6 cases, subtotally in 1 case, and partially in 2 cases. Meningioma was removed subtotally in 4 cases, partially in 3 cases, and less than 50% in 1 case. Other tumors (cholesteatoma, craniopharyngioma, fibrous dysplasia, giant cell tumor, glioma of the neurohypophysis, osteoma, plasmacytoma, carcinoid tumors, chondroma) were removed totally in 7 cases and subtotally in 7 cases. Postoperative cerebrospinal fluid leakage occurred in 9 (7.2%) cases, and meningitis developed in 12 (9.4%) cases. Oculomotor disorders occurred in 17 (13.4%) patients; in 10 of these patients, the disorders regressed within 4 to 38 days after surgery; in 7 patients the oculomotor disorders did not regress. A lethal outcome occurred in 2 (1.57%) cases.

Conclusion. The extended endoscopic endonasal posterior transclival approach, being minimally invasive, enables removal of various midline skull base tumors with/without involvement of the clivus with high radicalness, low risk of postoperative complications, and low lethality. Until recently, these tumors were considered almost inoperable.

Keywords: endoscopic transclival approach, endoscopic endonasal skull base surgery, clivus, clival chordoma, endoscopic monitoring of cranial nerves.

Abbreviations:
ACTH — adrenocorticotropic hormone
MR angiography — magnetic resonance angiography
MRI — magnetic resonance imaging
SCT angiography — spiral computed tomography angiography
DM — dura mater

To date, there are a quite large number of anterior approaches to the clivus (transoral, transphenoidal, transmaxillary, transfacial, transbasal, transtemporal). Some of these require an extensive resection of the facial, cranial, intraoral, and intranasal structures [1—10]. W. Couldwell et al. [3] assessed the capabilities and disadvantages of each of the approaches. An obvious advantage of the endoscopic transnasal approach, which was introduced in clinical practice later, is that it can be used to access almost the whole skull base and craniovertebral junction, from the posterior ethmoid cells to the axis, and allow the surgeon to remove tumors with minimal impact on the brainstem structures.

The development of the modern endoscopic technique has been accompanied by reports from the world’s leading clinics on experience in surgical removal of midline skull base tumors using the endoscopic transclival approach (Table 1) [11—15]. According to J. Sanmillan et al. [16], the results of application of the endoscopic transclival approach in removal of midline skull base tu-
mors are comparable to those obtained with various transcranial approaches, and even exceed them in some cases.

The clivus is conventionally divided into three portions (thirds) in order to facilitate the choice of a particular surgical approach [17, 18]. The upper clivus corresponds to the dorsum sellae region that extends from the posterior clinoid processes to the Dorello canal level. The upper clivus also corresponds to the posterior wall of the sphenoid sinus [19, 20]. The middle clivus is located between the Dorello canal level and the pars nervosa of the jugular foramen; the lower clivus extends from the pars nervosa of the jugular foramen to the foramen mag-

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Stamm et al.</td>
<td>2011</td>
<td>23</td>
</tr>
<tr>
<td>P. Gardber, C. Snyderman</td>
<td>2012</td>
<td>60*</td>
</tr>
<tr>
<td>Ede A. Silva Vellutini</td>
<td>2014</td>
<td>38</td>
</tr>
<tr>
<td>T. Tamura</td>
<td>2015</td>
<td>24</td>
</tr>
<tr>
<td>O. Al-Mefty**</td>
<td>2008</td>
<td>43</td>
</tr>
</tbody>
</table>

Footnote. *Information on the use of the transclival approach by some of the world leaders in endoscopic skull base surgery, P. Gardner and S. Snyderman, was provided in their personal communication. ** The author used the endoscopically assisted transclival approach.

Fig. 1. Clival portions (the upper, middle, and lower clivus is shown in pink-red, yellow, and green, respectively).

a — inner surface of the clivus: 1 — left petrous apex of the temporal bone, 2 — left oval foramen, 3 — left jugular foramen, 4 — opening of the internal auditory canal;
b — outer surface of the clivus: 1 — posterior ethmoid cells, 2 — left round foramen, 3 — right round foramen, 4 — pharyngeal tubercle, 5 — right oval foramen, 6 — left greater wing of the sphenoid bone, 7 — left inferior orbital fissure, 8 — right lesser wing of the sphenoid bone, 9 — right superior orbital fissure.

Diagram 1. Distribution of tumors by histological pattern.
num [17, 18]. The Dorello canal is formed by the petroclival ligament (Gruber) and inferior part of the posterior clinoid process (the abducens nerve and meningeal branch pass in the canal from the internal carotid artery to the clivus). The described conditional boundaries are more pronounced on the inner surface of the clivus. The boundary between the middle and lower clivus can only be identified on the outer surface of the clivus. The presented bony landmarks for identification of the clival levels are denoted in Figure 1a, b. More detailed anatomy of the clivus is presented in Part 1 of our paper [21].

The endoscopic endonasal posterior approach should be used to resect clival tumors located along the midline and above the hard palate (extradurally or intradurally).

### Material and methods

Since 2008, we operated on 127 patients (60 males and 67 females) with various skull base tumors located in the clival region using the extended endoscopic endonasal posterior (transclival) approach; the patients’ age ranged from 3 to 74 years (median, 46 years). The distribution of tumors by histology is shown in Diagram 1. The distribution of tumors by size is presented in Diagram 2: there were 36 (28.35%) giant (>60 mm), 71 (55.9%) large (35—59 mm), 19 (14.96%) medium (21—35 mm), and 1 (0.79%) small (<20 mm) tumors.

Twenty eight patients had previous surgery; of these: 11 transcranial interventions (7 at the Neurosurgical Institute (NSI) and 4 in other clinics), 16 endoscopic interventions (10 at the NSI and 6 in other clinics), and 1 transnasal microsurgery (NSI). The standard transnasal endoscopic approach to the sella turcica (histologically, all tumors were chordomas) was used in previous endoscopic operations.

Information on the location of tumors in the clival portions and spreading to the adjacent anatomical regions is presented in Tables 2 and 3.

All 127 patients underwent endoscopic endonasal transclival resection of midline clival tumors extending into the posterior cranial fossa. Before surgery, patients underwent a general clinical, ophthalmological, neurological, and endocrinological examination. All patients underwent high resolution CT in three projections; MRI with and without intravenous contrast, MR angiography, and SCT angiography were used to identify the relationships between the tumor and the main vessels. In 10 patients, we exploited intraoperative neuromonitoring of the cranial nerves using an original technique [22—24]. The Karnofsky scale was used to evaluate the health condition of patients. In the early postoperative period, a CT or MRI study was used to control the extent of tumor resection.

#### A technique of endoscopic endonasal transclival resection of clival and ventral posterior cranial fossa tumors

During an approach, the trepanation window should correspond to the clival region involved in the pathological process. The clivus is resected according to the anatomical landmarks using a high-speed drill with a spherical diamond-coated burr of 3 to 4 mm in diameter (a high-speed flexible drill is most suitable for this manipulation). Trepanation starts at the level of the sphenoid sinus floor. It should be performed very carefully near lateral boundaries of the approach, which are represented
### Table 4. Clinical picture before surgery and changes in symptoms after surgery

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of cases (% of the total number)</th>
<th>Normalization/ improvement, %</th>
<th>No change, %</th>
<th>Deterioration, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor disorders (one or combination of III, IV, and VI nerves)</td>
<td>86 (67.7)</td>
<td>66 (76.7)</td>
<td>13 (15.1)</td>
<td>7 (8.1)</td>
</tr>
<tr>
<td>V nerve dysfunction</td>
<td>43 (33.9)</td>
<td>40 (93)</td>
<td>2 (4.65)</td>
<td>—</td>
</tr>
<tr>
<td>Visual impairments</td>
<td>24 (18.9)</td>
<td>18</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Bulbar disorders (dysphagia/dysphonia)</td>
<td>35 (27.6)</td>
<td>28 (80)</td>
<td>5 (14.3)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>11 (8.7)</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>15 (11.8)</td>
<td>13</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Face asymmetry (VII nerve paresis)</td>
<td>11 (8.7)</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coordination disorders</td>
<td>21 (5.5)</td>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Brainstem symptoms (SNyHD&lt;, SNyHS&gt;)</td>
<td>7 (5.5)</td>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cerebral symptoms (headache)</td>
<td>50 (39.4)</td>
<td>50 (100)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>8 (6.3)</td>
<td>5</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Nasal breathing disorders</td>
<td>5 (3.9)</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydrocephalus (fundal congestion)</td>
<td>7 (5.5)</td>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sensory pathway disorders</td>
<td>4 (3.1)</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cognitive disorders (mental disorders)</td>
<td>7 (5.5)</td>
<td>6</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>3 (2.4)</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Footnote. *Arterial hypertension was caused by compression of the vasomotor center structures, which was almost resistant to drug therapy. Arterial hypertension regressed after surgery.*

### Table 5. Overall extent of tumor resection (according to the Frank scale, 2002)

<table>
<thead>
<tr>
<th>Resection extent</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total resection</td>
<td>76</td>
<td>59.84</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>34</td>
<td>26.77</td>
</tr>
<tr>
<td>Partial resection</td>
<td>16</td>
<td>12.61</td>
</tr>
<tr>
<td>Insufficient resection (less than 50%)</td>
<td>1</td>
<td>0.79</td>
</tr>
</tbody>
</table>

### Table 6. Tumor resection extent depending on the histological pattern

#### Table 6.1. Extent of chordoma resection (n=96)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>63</td>
<td>65.6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>23</td>
<td>23.96</td>
</tr>
<tr>
<td>Partial</td>
<td>10</td>
<td>10.42</td>
</tr>
</tbody>
</table>

#### Table 6.2. Extent of pituitary adenoma resection (n=9)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1</td>
</tr>
<tr>
<td>Partial</td>
<td>2</td>
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</tbody>
</table>

#### Table 6.3. Extent of meningioma resection (n=8)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>4</td>
</tr>
<tr>
<td>Partial</td>
<td>3</td>
</tr>
<tr>
<td>Insufficient</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Table 6.4. Extent of cholesteatoma resection (n=3)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Table 6.5. Extent of fibrous dysplasia resection (n=3)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Table 6.6. Extent of craniopharyngioma resection (n=2)

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2</td>
</tr>
</tbody>
</table>
**Fig. 2.1. Case 1. A 44-year-old male patient K.**

A giant dedifferentiated skull base chordoma extending from the dorsum sellae level to the lower clivus, grossly compressing the brainstem structures, and invading the mesencephalic regions of the brain with the development of occlusive hydrocephalus. a—d — preoperative MRI scans (in Figure A, the red straight arrow indicates the direction of the transnasal approach).

**Fig. 2.2. Case 1.**

a—c — intraoperative images. a — overall view of the surgical area after tumor resection: 1 — clival dura mater, 2 — decompressed portions of the pons, 3 — basilar artery, 4 — basilar trifurcation (to the left and right posterior cerebral arteries and right superior cerebellar artery), 5 — trunk of the right superior cerebellar artery, 6 — partially hypoplastic trunk of the left anterior inferior cerebellar artery, 7 — right posterior inferior cerebellar artery; b — upper parts of the surgical approach area; mesencephalic structures are seen: 1 — basilar artery trunk, 2 — left posterior cerebral artery, 3 — right posterior cerebral artery, 4 — right superior cerebellar artery, 5 — interpeduncular cistern area (covered by the arachnoid mater); c — lower parts of the surgical approach area; medulla oblongata structures are seen: 1 — basilar artery trunk, 2 — right posterior inferior cerebellar artery, 3 — left vertebral artery, 4 — right vertebral artery, 5 — curved aspirator.

**Fig. 2.3. Case 1.**

a—c — postoperative MRI scans (day 14 after surgery). d—f — postoperative SCT scans (day 14 after surgery). Total tumor resection and regression of occlusive hydrocephalus.
Fig. 3.1. Case 2. A 22-year-old female patient E. A giant skull base chordoma grossly compressing the medulla oblongata and midbrain.
a—e — preoperative MRI scans (in Figures A and B, the red straight arrow indicates the direction of the transnasal approach; in Figures C and D, the red arched arrow indicates the direction of the approach to the posterior part of the tumor around the brainstem structures; in Figure C, the yellow arrow indicates the basilar artery).

Fig. 3.2. Case 2.
a—d — MRI scans 12 months after surgery: subtotal tumor resection.

Fig. 4. Case 3. A 63-year-old female patient P. A giant meningioma of the clival region and left cerebellopontine angle.
a, b — preoperative MRI scans (in Figure A, the red straight arrow indicates the direction of transnasal approach); c, d — MRI scans 4 months after surgery: subtotal tumor resection.
Fig. 5. Case 4. A 40-year-old male patient Zh. A giant prolactin-secreting pituitary adenoma.

Table 7. Postoperative complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve insufficiency*:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>3.15</td>
</tr>
<tr>
<td>VI</td>
<td>13</td>
<td>10.2</td>
</tr>
<tr>
<td>IX, X</td>
<td>1</td>
<td>0.79</td>
</tr>
<tr>
<td>Liquorrhea</td>
<td>1</td>
<td>0.79</td>
</tr>
<tr>
<td>Liquorrhea + meningitis</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td>Meningitis</td>
<td>4</td>
<td>3.15</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>1</td>
<td>0.79</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Lethal outcome</td>
<td>2</td>
<td>1.57</td>
</tr>
</tbody>
</table>

Footnote. *Cranial nerve dysfunction developed after surgery. Cranial nerve dysfunction regressed in 10 patients within 1 to 4 months.

by the optic nerve canals, cavernous segments of the internal carotid arteries, and abducens nerves. The maximum lateral limits of the approach at the upper clivus level are about 16 mm. As trepanation proceeds, the approach boundaries are extended in the caudal direction: they are 34 mm at the hypoglossal canal level and 20 mm between the abducens nerves. The vertical dimension between the sella turcica floor and the inferior edge of the clivus is 30 mm, and the thickest part of the clival bone is 18 mm rostrally and 8 mm caudally. Extensive trepanation of the clivus provides a larger access area, improves visualization, and facilitates manipulations with vital anatomical structures [25—27]. This is described in more detail in Part 2 of our paper [28]. When approaching the petrous apex of the temporal bone, a neuronavigation system should be used due to the proximity of the petrous internal carotid arteries. In the case of preserved clival bone tissues, trepanation was performed within the limits necessary to remove the tumor. If the clival bone was partially destroyed by the tumor, the altered bone structures were resected until visually intact bone tissue. In rare cases, the clival bone in the area affected by the tumor (chordoma) may be absent at all. After trepanation of the clivus, the DM is opened with a linear incision (the DM is more often intact). Extradural and intradural parts of the tumor are removed using special vacuum aspirators, curettes, and various forceps. An ultrasonic disintegrator is used for solid tumors (chordomas, meningiomas, etc.). Various endoscopes (0, 30, 45, or 70°) can be sequentially used for visualization at different stages of surgery. Bleeding from the cavernous sinus or basilar venous plexus, and often from both structures simultaneously, can be controlled with hemostatic foam (Surgiflow). It is extremely important to spare small vascular branches extending from the main vessels (basilar, posterior cerebral, and vertebral arteries). If a very dense tumor fragment cannot be separated from the main vessel, the fragment should be preserved to avoid life-threatening bleeding or ischemia of the brainstem structures. If the tumor extends intradurally, the DM is opened for tumor resection, but sometimes, the DM is initially destroyed by the tumor (chordomas). In these cases, the DM and skull base defect are repaired using a flap from the fascia lata, adipose tissue of the thigh, and bone and cartilaginous parts of the nasal septum or fibrin-thrombin glue.

In some cases, DM was repaired using microsutures according to a technique developed and patented by the authors [29, 30].

In the case of chordomas and other tumors, the tumor was considered to be completely resected if there were no signs of the mass on control contrast-enhanced MRI or CT scans. The extent of tumor resection was assessed using a scale by G. Frank and E. Pasquini [31]:

- radical or total resection: no tumor signs on control CT and MRI scans;
- subtotal resection: the remaining tumor volume is less than 20% of the initial tumor size;
- partial resection: the remaining tumor volume is less than 50% of the initial tumor size;
- insufficient resection: the remaining tumor volume is 50% or more of its initial size.

In the case of cholesteatoma, resection was considered complete if the tumor was resected together with its capsule. However, given the spreading pattern of these tumors as well as a pronounced adhesive process that often occurred due to aseptic inflammation, resection of...
the capsule was not always possible. In fibrous dysplasia, the extent of resection was assessed based on the boundaries of visually intact bone tissue and control SCT scans. Data on the extent of resection of different tumors are presented in Tables 5 and 6.

Figure 2 (2.1—2.3) presents a case of a patient with a giant dedifferentiated chordoma of the skull base (case 1). A general view of the surgical field after trepanation of the upper, middle, and lower clivus and tumor resection, the brainstem structures, main vessels located in the projection of appropriate clival regions, and preoperative and postoperative images are presented.

Another three illustrative examples (cases 2—4) are shown in Figures 3—5.

Results

Evaluation of changes in the clinical picture of the disease before and after surgery is presented in Table 4. Oculomotor disorders (impaired function of one or a combination of the IIIrd, IVth, and VIth cranial nerves) before surgery were detected in 86 (67.7% of the total number) patients; the oculomotor disorders regressed in the early postoperative period in 66 (76.7%) patients;
### Table 8. Changes in the clinical picture in patients who underwent cranial nerve monitoring

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, gender</th>
<th>Histologic diagnosis</th>
<th>Location</th>
<th>Tumor size</th>
<th>Clinical picture of surgery (oculomotor function score in points)</th>
<th>Type of endoscopic transnasal approach</th>
<th>Resection extent</th>
<th>Identified cranial nerves</th>
<th>M-response pattern</th>
<th>Changes in symptoms in the postoperative period (oculomotor function score in points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 years, M</td>
<td>Chordoma</td>
<td>Clivus</td>
<td>Large</td>
<td>III nerve paresis, left, and VI nerve insufficiency, right (4 points upward, 1 point downward, 2 points outward, 1 to 2 points inward)</td>
<td>Transclival</td>
<td>Total</td>
<td>III nerve bilaterally, left VI nerve</td>
<td>D 1 S 0 D S 0</td>
<td>Improvement: 5 points upward, 3 points downward, 2 points inward, 1 to 2 points outward</td>
</tr>
<tr>
<td>2</td>
<td>66 years, M</td>
<td>Chordoma</td>
<td>Clivus</td>
<td>Large</td>
<td>Left hemiparesis: upper limb - 2, lower limb - 3. Insufficiency of V, n.sin. and VII, n.sin., hemihypesthesia, left</td>
<td>Transclival</td>
<td>Total</td>
<td>III nerve bilaterally, right VI nerve</td>
<td>D 1 S 1 D S 1</td>
<td>Partial regression of left-sided hemiparesis: upper limb - 3, lower limb - 4 points. Persistent insufficiency of VII n., left</td>
</tr>
<tr>
<td>3</td>
<td>26 years, F</td>
<td>Chordoma</td>
<td>Clivus and left cavernous sinus</td>
<td>Large</td>
<td>Insufficiency of V, n.sin. and VI, n.sin.</td>
<td>Transclival + extended lateral</td>
<td>Total</td>
<td>Left III nerve</td>
<td>D 1 S 1 D S 1</td>
<td>Partial regression of VI n. insufficiency, left</td>
</tr>
<tr>
<td>4</td>
<td>65 years, M</td>
<td>Chordoma</td>
<td>Endosupra-infrasellar</td>
<td>Large</td>
<td>Headache</td>
<td>Transclival + extended bilateral</td>
<td>Total</td>
<td>VI nerve bilaterally</td>
<td>D S 1 D S 1</td>
<td>Headache regression</td>
</tr>
<tr>
<td>5</td>
<td>20 years, F</td>
<td>Chordoma</td>
<td>Giant</td>
<td>Insufficiency of VI nerve, left</td>
<td>Transclival</td>
<td>Total</td>
<td>VI nerve bilaterally</td>
<td>D S 1 D S 1</td>
<td>Partial regression of VI n.s. insufficiency</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>67 years, F</td>
<td>Chordoma</td>
<td>Clivus</td>
<td>Giant</td>
<td>Paresis of VI n.sin.</td>
<td>Transclival</td>
<td>Total</td>
<td>Left VI nerve, left VI nerve</td>
<td>D S 1 D S 1</td>
<td>Partial regression of VI nerve paresis, left</td>
</tr>
<tr>
<td>7</td>
<td>31 year, M</td>
<td>Chordoma</td>
<td>Clivus</td>
<td>Large</td>
<td>Brainstem symptoms (nystagmus), Insufficiency of VI nerve, left</td>
<td>Transclival</td>
<td>Total</td>
<td>left VI nerve</td>
<td>D S 1 D S 1</td>
<td>No changes. Regression of cranial pain syndrome</td>
</tr>
<tr>
<td>8</td>
<td>26 years, M</td>
<td>Chordoma</td>
<td>Clivus</td>
<td>Medium</td>
<td>Insufficiency of VI nerve, left</td>
<td>Transclival</td>
<td>Total</td>
<td>VI nerve bilaterally</td>
<td>D S 1 D S 1</td>
<td>Regression</td>
</tr>
<tr>
<td>9</td>
<td>62 years, F</td>
<td>Meningioma</td>
<td>Clivus</td>
<td>Giant</td>
<td>Insufficiency of XII nerve, right</td>
<td>Transclival</td>
<td>Subtotal</td>
<td>Left VI nerve</td>
<td>D S 1 D S 1</td>
<td>Regression of XII nerve insufficiency, right</td>
</tr>
<tr>
<td>10</td>
<td>33 years, F</td>
<td>Cholesteatoma</td>
<td>Clivus</td>
<td>Giant</td>
<td>Insufficiency of V, VII, VIII, and X nerves, left</td>
<td>Transclival</td>
<td>Subtotal</td>
<td>Left III, VI, VII, and XII nerves</td>
<td>D S 1 D S 1</td>
<td>Worsening of VI nerve paresis, left, less pronounced paresis of left III nerve, persistent insufficiency of left VII and V</td>
</tr>
</tbody>
</table>

**Footnote.** *M-response patterns: — no response, 0 — weak response, 1 — strong response.*
there were no changes in 13 (15.1%) patients; worsening (loss of the function of these nerves) occurred in 7 (8.1%) patients. Impairments of the trigeminal nerve function (mainly in the form of hypoesthesia) manifested in 44 (33.9%) patients; hypoesthesia regressed in 40 (93%) patients; there were no changes in 2 (4.65%) patients. Visual disorders (visual field impairment, reduced visual acuity) were present in 24 (18.9%) patients, which regressed in 18 patients and did not change in 6 cases. Fudal congestion signs in the form of optic disc edema and moderate venous congestion were detected in 7 patients with hydrocephalus, which regressed in the postoperative period. Preoperative bulbar disorders were detected in 35 (27.6%) patients; in 28 (80%) of these, regression of symptoms was observed; there were no changes in 5 (14.3%) patients; deterioration occurred in 2 (5.7%) patients. Motor disorders in the form of hemiparesis (decreased strength) in the extremities were present in 11 (8.7%) patients; in all patients, symptoms completely regressed after surgery. Dysfunction of the auditory portion of the VIIIth nerve in the form of hearing loss was detected in 15 (11.8%) patients; in all cases, symptoms regressed after surgery. Dysfunction of the facial nerve was detected in 11 patients; complete regression of symptoms occurred in all cases. Cerebellar disorders in the form of coordination disorders were present in 21 (16.5%) patients; the disorders regressed in all patients after surgery. Brainstem symptoms in the form of horizontal nystagmus were found in 7 (5.5%) patients, which also completely regressed after surgery. Before surgery, 50 (39.4%) patients had cerebral symptoms (headache) that regressed in 100% of cases after surgery. In 5 patients, the tumor extended to the nasopharynx, causing nasal breathing impairment; after surgery, the breathing was normalized. Endocrine disorders were detected in 8 (6.3%) patients; the function normalized in 5 patients and deteriorated in 3 patients. Oclusive hydrocephalus was detected in 7 (5.5%) patients, which regressed in all of them. Sensory pathway disorders were detected in 4 (3.1%) patients. Mental disorders occurred in 7 (5.5%) patients; in 6 patients, they regressed; the symptoms deteriorated in 1 case. The most rare symptom was arterial hypertension (caused by compression of the brainstem structures by a tumor), which developed in the form of a “crisis” and was practically resistant to drug therapy. After surgery, arterial hypertension regressed in all 3 cases.

The extent of tumor resection was evaluated according to the G. Frank scale [31]. Tables 5 and 6.1—6.6 present the data on the total radicalness as well as the radicalness of resection according to the histological structure of tumors (chordomas, pituitary adenomas, meningiomas, cholesteatomas, fibrous dysplasias, craniopharyngiomas).
The extent of resection of other singly detected tumors was as follows: giant cell tumor and carcinoid — subtotal resection; plasmacytoma, osteoma, glioma of the neurohypophysis, and chondroma — total resection.

The main complications in the postoperative period (Table 7) were oculomotor disorders, with abducens nerve dysfunction being the most common disorder (13 patients; in 8 patients, the dysfunction regressed within 1 to 4 months after surgery; persistent neurological deficit occurred in 5 patients); oculomotor nerve paresis was present in 4 patients (in 2 patients, the symptoms regressed within 2 to 3 months after surgery, and the deficit was persistent in 2 patients). Liquorrhea was present in 9 (7.1%) patients; meningitis was detected in 5 (3.9%) patients; in 8 patients, the dysfunction regressed within 1 to 20 points. In the remaining 11% (n=14) patients, a change in the Karnofsky index changed by 14.18 points and amounted to 85.91. In 17 (29.13%) patients, the index reaches 100, which indicates an improvement in the patients’ condition.

Disease recurrence (mainly due to continued tumor growth) occurred in 17 patients (15 patients with chor- doma, 1 patient with meningioma, and 1 patient with fibrous dysplasia), which required repeated surgery in a period of 17 months to 10 years (median, 22.7 months) after the first surgery.

Figure 7 presents the results of a statistical analysis of the Karnofsky index dynamics in the form of a histogram (calculations were made using the Statistica 10 software; the confidence interval of the study was 99%; the significance level was $p<0.01$). The histogram displays the absolute value of the difference ($\Delta K$) between Karnofsky index values after and before surgery ($\Delta K=K_{after\ surgery}-K_{before\ surgery}$, where $K$ is the Karnofsky index). The red color in the graph denotes the number of cases (patients) with an improvement in the Karnofsky index ($\Delta K>0$) ($n=108$; 85.04%). The absence of improvement in the Karnofsky index ($\Delta K=0$) was observed in 16 patients, which accounted for 12.6% of the total number of patients (yellow column in the histogram). Deterioration of the Karnofsky index ($\Delta K$) is indicated in the histogram by a green column ($n=1$; 0.79%). The blue column in the histogram indicates clinical cases with a lethal outcome ($n=2$; 1.57%).

In most patients ($n=94$; 74%), a change in the index amounted to 10—20 points. In the remaining 11% ($n=14$) patients, a change in the Karnofsky index was 30—60 points. Thus, the mean Karnofsky index changed by 14.18 points and amounted to 85.91. In 37 (29.13%) patients, the index reaches 100, which indicates an improvement in the patients’ condition.

Conclusion

Midline skull base tumors have a hard-to-reach location for surgery through standard transcranial approaches, and only their partial resection is usually possible. In addition, palliative interventions and shunting surgery for resolving of hydrocephalus and decompression of the posterior cranial fossa structures were previously performed. The extended endoscopic endonasal posterior (transclival) approach, being minimally invasive, enables surgical removal of various midline skull base tumors with involvement of the clivus, which until recently were considered hard-to-reach for surgical treatment. The tumors can be resected with high radicalness, low risk of postoperative complications, and low lethality. These advanced operations should be performed in highly specialized hospitals where neurosurgeons have sufficient experience in both endoscopic and microsurgical operations on various skull base structures.

Authors declare no conflict of interest.
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2. Konovalov AN, Sidorkin DV, Shkarubo AN, Usachev DYU, Mahmudov UB. Hormony osnovaniya cherepa i kraniovertebral'nogogo perechoda. M. (In Russ.).


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Commentary

The reviewed article is the logical conclusion of a series of scientific and practical studies and publications devoted to detailed investigation of the topographic and anatomical features of the clivus and its adjacent structures for the purpose of clinical application of a minimally invasive endoscopic transclival approach to clival and ventral posterior cranial fossa tumors. The study completely meets the Journal’s scope. The Abstract is well structured and fully reflects the article’s matter. A careful analysis of modern domestic and foreign literature substantiates high topicality of this issue, which is convincingly presented in the Introduction. The authors critically analyze the current scientific information on this issue, which is available in the world literature. The article describes in detail the topographic anatomy and stages of the proposed surgical approach, its technical advantages, and possible complications. The article contains high quality illustrations, clinical examples, informative and illustrative figures, and diagrams presenting the obtained statistical data. It should be noted that the clinical experience accumulated by the authors is currently the largest one in the world. The article indicates a high scientific and methodological level of conducted research and the great practical significance of its results. The study convincingly proves that the extended endoscopic endonasal posterior (transclival) approach can be safely used for surgical treatment of patients with clival lesions, accessing neoplasms of the anterior portions of the posterior cranial fossa, and is an alternative to transcranial approaches. The study is original, well thought out, and logically complete. Due to a large sample size, the mathematical results of the study are statistically reliable. Based on the objective data obtained by the authors, the transclival approach can be successfully used in clinical practice. The study is certainly a new step in the development of modern minimally invasive neurosurgery. It is necessary to note a high international level of scientific and practical activity of the authors in this complex field of neurosurgery. The theoretical and practical results of conducted innovation research are of considerable interest both for neurosurgeons and for specialists in related fields.

Yu.A. Shcherbak (St. Petersburg, Russia)
In spine surgery, acute and chronic postoperative pain (CPP) is a challenge. After spine surgery, severe pain syndrome often develops, and about 15—45% of patients has experienced pain for months and years after surgical treatment [1, 2]. At the same time, typical surgical interventions in different people are known to cause pain of different intensity [3]. Prognostic parameters for the severity of acute as well as chronic pain syndrome (CPS) in spine surgery have not been defined yet. Probably, early identification of these risk factors could further help in selection of patients for surgical treatment as well as in development of differentiated protocols for perioperative analgesia, treatment, and rehabilitation.

The study purpose was to reveal prognostic parameters for the severity of acute dynamic pain on the 1st postoperative day and CPS 5—7 months after surgery.

Material and methods

The prospective study included 291 patients. The study was approved by the local ethics committee of the Sklifosovsky Research Institute of Emergency Medicine. The patients underwent elective surgery for degenerative diseases and injuries of the spine in 2010—2016. The study included all patients aged 18 to 70 years with ASA grade I to III physical status who did not meet exclusion criteria and were preparing for elective surgery for degenerative disease or injury of the spine in the Neurosurgery Department.

The exclusion criteria were as follows: 1) a history of previous lumbar or thoracic spine surgery; 2) complicated or combined traumatic spinal cord injury (TSCI); 3) problems of communication with the patient; 4) a history of allergic reactions to certain analgesics; 5) contraindications to the use of non-steroidal anti-inflammatory drugs, paracetamol, and opioid analgesics; 6) refusal to participate in the study.

Patients were excluded from the study also if they did not comply with the study protocol or refused to take analgesics. Patients who received regional anesthesia were excluded from the study if the dura mater was damaged during surgery because the use of regional anesthesia put them at the risk of an unpredictable spinal block.

Of the 291 patients included in the study, 129 (57 males and 72 females) subjects underwent lumbar discectomy for intervertebral disc herniation (IDH); 122 patients (55 males and 67 females) underwent decompression of neural structures and fixation of the spine with a cage and transpedicular system for lumbar spinal canal stenosis (SCS); 40 patients (23 males and 17 females) underwent decompression and fixation of the lumbar and/or thoracic spine for TSCI.

During a preoperative examination, an anesthesiologist instructed a patient to use a 10-cm visual analogue pain scale (VAS), with the 0 cm mark meaning no pain...
and the 10 cm mark being unbearable pain. Sociodemographic factors (gender, age, body mass index, education level (secondary/specialized secondary/higher education — se/see/hi), smoking, and clinical data (intensity of pain at rest and during motion, its duration and regularity, frequency of taking analgesics) were collected. The psychological status of patients was analyzed: the expected intensity of postoperative pain was determined by using VAS; the degree of situational anxiety (SA) and personal anxiety (PA) was determined according to the Spielberger anxiety scale — State-Trait Anxiety Inventory (STAI) [4]; the depression degree was assessed by using the Beck Depression Inventory (BDI) [5]; the kinesiophobia degree was determined with the Tampa Scale of Kinesiophobia (TSK-17) [6]; the degree of catastrophizing was evaluated by using the Pain Catastrophizing Scale (PCS) [7]. The pain threshold (PT) and pain tolerance (PTT) were assessed using a mechanical algometer (Wagner Force Ten Digital Force Gauge FPX 50, Wagner Instruments, USA).

All interventions were performed by five surgeons who had at least 5 year experience in spine surgery. The type of anesthesia was chosen by an anesthesiologist and a patient. Anesthesia was conducted by a group of 3 anesthesiologists supervised by a senior anesthesiologist who had many years of experience in neuroanesthesia. Most patients (268 subjects) were operated on under general anesthesia using sevoflurane inhalation, fractional intra-venous administration of fentanyl, and myoplegia with non-depolarizing neuromuscular relaxants. Spinal anesthesia with bupivacaine was used in 23 patients with IDH. In some patients, general anesthesia was supplemented with regional anesthesia. In 54 patients (22 SCS and 32 TSCI patients), prolonged epidural anesthesia was used; in 45 IDH patients, infiltration with bupivacaine solution was performed before wound closure; in 20 SCS patients, intraoperative wound infiltration with ropivacaine solution was combined with prolonged post-operative wound irrigation with ropivacaine and ketorolac solution. After completing surgery, all patients were extubated on the operating table and, after restoration of clear consciousness, transferred to a ward of the Neurosurgery Department (IDH patients) or an intensive care ward (patients with SCS and TSCI). Postoperative analgesia was also multicomponent and was based on the WHO pain ladder principles [6]. In 47 patients, “on-demand” analgesia was used, with a particular analgesic being prescribed by an attending or on duty doctor. Various regimens of preventive multimodal analgesia on the basis of non-steroidal anti-inflammatory drugs, paracetamol, nefopam, pregabalin, and regional anesthesia were prescribed by an anesthesiologist to 244 patients. In the case of an insufficient efficacy of basic non-opioid analgesia, patients could independently administer nalbuphine (IDH patients) or morphine (patients with SCS and TSCI) through a syringe dispenser using a patient-controlled analgesia technique.

The intensity of postoperative pain was assessed during motion (turning in the bed, walking) by using VAS. On the day of surgery, the pain was assessed every 2 h for 12 h, and then the median and interquartile range (25th and 75th percentile) for the 1st day were calculated for each patient. Pain was considered mild or significant if the median of pain intensity (VAS) was in a range of 0—4 cm or 5—10 cm, respectively. To determine the long-term surgical treatment outcomes, patients reported pain in their back and/or lower limb during a telephone interview 5—7 months after surgery. Repeated surgery within 5—7 months after enrollment in the study was the basis for exclusion of a patient from the study at the telephone survey stage.

A statistical analysis of the data was performed using the Statistica 9.1 software (StatSoft Inc., USA). Descriptive statistics of quantitative indicators is represented by medians and quartiles, and that of qualitative indicators is represented by absolute and relative frequencies. The 95% confidence interval (CI) was calculated for some relative frequencies. Quantitative indicators were compared in two independent groups using the Mann-Whitney test, and qualitative indicators were compared using the χ2 criterion and exact Fisher test. Spearman rank correlation was used to correlate the indicators. A direct stepwise logistic regression was used for development of prognostic models. The missing values (less than 10% for each of the variables) were replaced by medians: the parameter of hourly pain intensity on the 1st day was replaced by the median per day for a given patient; the remaining indicators were replaced by medians for specific pathologic groups (IDH, SCS, or TSCI). Two prognostic models were developed: the likelihood of acute dynamic pain on the 1st postoperative day and the likelihood of chronic pain at 5—7 months after surgery. The quality of models was evaluated using the Hosmer-Lemeshow criterion, and the adequacy of models was evaluated based on point and interval (95% CI) estimates of prognosis efficiency indicators. A significance threshold level was set to p=0.05.

Results

During the 1st postoperative day, 114 (39%) patients reported significant dynamic pain, and 177 (61%) patients reported mild dynamic pain. Among patients with significant dynamic postoperative pain, there were statistically significantly more SCS patients and less IDH patients, which may be explained by greater invasiveness of SCS surgery. In addition to the main pathology, patients with mild and significant dynamic postoperative pain had statistically significant differences in 8 variables: gender, intensity of static and dynamic pain before surgery, expectation of postoperative pain, SA, PA, PT, and PTI (Table 1).

Then, we generated a mathematical model for predicting dynamic pain on the 1st postoperative day (sig-
Table 1. Characterization of patients with mild and significant dynamic pain on the 1st postoperative day

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Mild pain (n=177)</th>
<th>Significant pain (n=114)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, m/f, %</td>
<td>54/46</td>
<td>35/65</td>
<td>0.003*</td>
</tr>
<tr>
<td>Age, years, Me (UQ; LQ)</td>
<td>49 (38; 56)</td>
<td>52 (42; 61)</td>
<td>0.063**</td>
</tr>
<tr>
<td>Body mass index, kg/m², Me (UQ; LQ)</td>
<td>28 (25; 32)</td>
<td>28 (24; 31)</td>
<td>0.366**</td>
</tr>
<tr>
<td>Education level, se/sce/he, %</td>
<td>11/33/57</td>
<td>11/37/52</td>
<td>0.723***</td>
</tr>
<tr>
<td>Smoking, yes/no, %</td>
<td>42/58</td>
<td>37/63</td>
<td>0.385*</td>
</tr>
<tr>
<td>IDH, yes/no, %</td>
<td>51/49</td>
<td>37/63</td>
<td>0.045*</td>
</tr>
<tr>
<td>SCS, yes/no, %</td>
<td>35/65</td>
<td>54/46</td>
<td>0.002*</td>
</tr>
<tr>
<td>Pain at rest (VAS), cm, Me (UQ; LQ)</td>
<td>1.5 (0; 3.5)</td>
<td>3 (0.5; 5)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Motion pain (VAS), cm, Me (UQ; LQ)</td>
<td>4.5 (2; 6.5)</td>
<td>6.5 (4; 8)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Pain duration, months, Me (UQ; LQ)</td>
<td>6 (2.5; 36)</td>
<td>10 (3; 36)</td>
<td>0.130**</td>
</tr>
<tr>
<td>Periodicity of pain, (no/≤ 2 days per week/&gt;2 days per week/every day/ constantly)</td>
<td>7/3/9/48/33</td>
<td>4/1/4/52/39</td>
<td>0.222***</td>
</tr>
<tr>
<td>Frequency of taking analgesics, % (no/≤ 2 days per week/&gt;2 days per week/every day/ constantly)</td>
<td>53/5/11/31</td>
<td>56/6/10/28</td>
<td>0.830***</td>
</tr>
<tr>
<td>Pain threshold, H, Me (UQ; LQ)</td>
<td>31 (23; 45)</td>
<td>29.5 (20; 39)</td>
<td>0.046**</td>
</tr>
<tr>
<td>Pain tolerance, H, Me (UQ; LQ)</td>
<td>72 (54.6; 92.4)</td>
<td>63.5 (46; 82)</td>
<td>0.012**</td>
</tr>
<tr>
<td>Expected pain (VAS), cm</td>
<td>4.5 (2.5; 6)</td>
<td>5.5 (4; 7.5)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>SA score</td>
<td>26 (21; 30)</td>
<td>28 (24; 37)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>PA score</td>
<td>41 (35; 49)</td>
<td>45 (39; 51)</td>
<td>0.006**</td>
</tr>
<tr>
<td>Depression score</td>
<td>10 (6; 14)</td>
<td>11 (8; 16)</td>
<td>0.056**</td>
</tr>
<tr>
<td>Kinesiophobia score</td>
<td>42.5 (40; 46)</td>
<td>43.5 (40.5; 48)</td>
<td>0.100**</td>
</tr>
<tr>
<td>Pain catastrophizing score</td>
<td>18 (13; 28)</td>
<td>21 (14; 29)</td>
<td>0.493**</td>
</tr>
</tbody>
</table>

Footnote. * — Comparison of groups using the Fisher exact test; ** — comparison of groups using the Mann-Whitney test; *** — comparison of groups using \( \chi^2 \).

Table 2. Parameters of a multinomial logit regression prognostic model for calculating the likelihood of mild dynamic pain on the 1st postoperative day (n=291)

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Regression coefficient ( \beta )</th>
<th>Standard error</th>
<th>Wald criterion ( \chi^2 )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motion pain before surgery (VAS), cm</td>
<td>–0.174467</td>
<td>0.047</td>
<td>13.497</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Expected pain (VAS), cm</td>
<td>–0.141624</td>
<td>0.051</td>
<td>7.828</td>
<td>0.005</td>
</tr>
<tr>
<td>Pain threshold, H</td>
<td>0.015794</td>
<td>0.008</td>
<td>4.184</td>
<td>0.041</td>
</tr>
<tr>
<td>Gender (1 — f, 2 — m)</td>
<td>–0.273542</td>
<td>0.133</td>
<td>4.245</td>
<td>0.039</td>
</tr>
<tr>
<td>Constant</td>
<td>1.555729</td>
<td>0.429</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

As an initial set of prognostic parameters, we used indicators characterized by statistically significant differences between the groups. Before generating a regression model, the above prognostic variables were examined for collinearity. The prognostic parameters with moderate and strong correlations were pain at rest and during motion before surgery (\( R=0.607, p<0.001 \)), SA and PA (\( R=0.825, p<0.001 \)), and PT and PT1 (\( R=0.615; p<0.001 \)). One variable was selected from each pair of correlated variables: pain during motion before surgery, SA, and PT. The parameters of pain intensity during motion and SA were preferred because they had a stronger correlation with the response variable, and the PT evaluation method was preferred because it was easy-to-use and comfortable for the patient (compared to TPI evaluation). Thus, 5 potential prognostic parameters were studied. Application of the direct stepwise procedure led to exclusion of the SA parameter from the regression model. The resulting multinomial logit regression model for the likelihood of mild dynamic postoperative pain, which includes 4 prognostic parameters, is presented in Table 2. The model includes 4 statistically significant prognostic parameters.

The likelihood of mild dynamic postoperative pain on the 1st day after surgery for degenerative diseases and injuries of the spine can be calculated by the formula:

\[
P = \frac{1}{1 + e^{-Y}}
\]

where: \( Y = 1.556 - 0.174 \times MP - 0.142 \times EP + 0.016 \times PT - 0.273 \times G \), MP is motion pain, EP is expected pain intensity, PT is the pain threshold, and G is the gender.

Correspondingly, the likelihood of significant pain is \( 1-P \). This model was implemented as a calculator in MS Excel. The model quality was good (the Hosmer-
Lemeshow criterion was 4.322; \( p=0.827 \). The classification matrix is shown in Table 3.

Table 3. Classification matrix of a logit regression model for predicting dynamic pain severity on the 1st postoperative day

<table>
<thead>
<tr>
<th>Simulation results</th>
<th>Significant pain (( n=114 ))</th>
<th>Mild pain (( n=177 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant pain (( n=83 ))</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>Mild pain (( n=208 ))</td>
<td>63</td>
<td>145</td>
</tr>
</tbody>
</table>

Table 4. Characterization of patients with and without chronic pain syndrome 5—7 months after surgery

<table>
<thead>
<tr>
<th>Study variable</th>
<th>No CPS (( n=99 ))</th>
<th>CPS (( n=173 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, m/f, %</td>
<td>55/45</td>
<td>41/59</td>
<td>0.004*</td>
</tr>
<tr>
<td>Age, years, Me (UQ; LQ)</td>
<td>48 (36; 55)</td>
<td>51 (41; 60)</td>
<td>0.006**</td>
</tr>
<tr>
<td>Body mass index, kg/m2, Me (UQ; LQ)</td>
<td>27 (24; 31)</td>
<td>28 (25; 31)</td>
<td>0.399**</td>
</tr>
<tr>
<td>Education level, se/se/he, %</td>
<td>9/32/59</td>
<td>11/35/54</td>
<td>0.695***</td>
</tr>
<tr>
<td>Smoking, yes/no, %</td>
<td>41/59</td>
<td>39/61</td>
<td>0.897*</td>
</tr>
<tr>
<td>Indications for surgery, IDH/SCS/TSCI, n</td>
<td>50/37/13</td>
<td>43/45/12</td>
<td>0.513***</td>
</tr>
<tr>
<td>Pain at rest before surgery (VAS), cm, Me (UQ; LQ)</td>
<td>1.5 (0; 3.5)</td>
<td>2 (0; 4.5)</td>
<td>0.051**</td>
</tr>
<tr>
<td>Motion pain before surgery (VAS), cm, Me (UQ; LQ)</td>
<td>4.5 (2; 6.5)</td>
<td>6 (3; 7.5)</td>
<td>0.024**</td>
</tr>
<tr>
<td>Pain duration, months, Me (UQ; LQ)</td>
<td>6 (3; 18)</td>
<td>8 (2.5; 36)</td>
<td>0.249**</td>
</tr>
<tr>
<td>Periodicity of pain, % (no/2 days per week/2 days per week/every day/continuously)</td>
<td>6/3/7/32/32</td>
<td>5/2/8/47/38</td>
<td>0.792***</td>
</tr>
<tr>
<td>Frequency of taking analgesics, % (no/2 days per week/2 days per week/every day)</td>
<td>64/4/9/22</td>
<td>49/6/11/34</td>
<td>0.103***</td>
</tr>
<tr>
<td>Pain threshold, H, Me (UQ; LQ)</td>
<td>31 (23; 41)</td>
<td>30 (22; 40)</td>
<td>0.339**</td>
</tr>
<tr>
<td>Pain tolerance, H, Me (UQ; LQ)</td>
<td>73 (53; 91)</td>
<td>67.5 (51; 89)</td>
<td>0.265**</td>
</tr>
<tr>
<td>Motion pain, 1st postoperative day (VAS), cm, Me (UQ; LQ)</td>
<td>2.75 (1.5; 4.75)</td>
<td>3.25 (2; 6)</td>
<td>0.015**</td>
</tr>
<tr>
<td>Expected pain (VAS), cm</td>
<td>4 (2.5; 6)</td>
<td>5 (3; 7)</td>
<td>0.024**</td>
</tr>
<tr>
<td>SA score</td>
<td>25 (21; 29)</td>
<td>27 (24; 33)</td>
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</tr>
<tr>
<td>PA score</td>
<td>40 (35; 47)</td>
<td>43 (36; 51)</td>
<td>0.036**</td>
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<td>Depression score</td>
<td>10 (6; 13)</td>
<td>11 (8; 16)</td>
<td>0.009**</td>
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<tr>
<td>Kinesiophobia score</td>
<td>43 (39; 47)</td>
<td>43 (40; 48)</td>
<td>0.735**</td>
</tr>
<tr>
<td>Pain catastrophizing score</td>
<td>17 (11; 22)</td>
<td>21 (13; 30)</td>
<td>0.124**</td>
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Footnote. * — Comparison of groups using the Fisher exact test; ** — comparison of groups using the Mann-Whitney test; *** — comparison of groups using \( \chi^2 \).

Then, we generated a mathematical model for predicting CPS 5—7 months after surgery (presence or absence of CPS). Indicators with statistically significant differences between groups were used as an initial set of prognostic factors. Before generating a regression model, the above prognostic variables were examined for collinearity. Prognostic indicators with moderate and strong correlations were SA and PA (\( R=0.827 \); \( p<0.001 \)). The SA indicator was preferred due to a stronger correlation with the response variable (compared to the estimate of PA). Therefore, 7 potential prognostic variables were studied. Application of the direct stepwise procedure led to exclusion of all the parameters from the regression model, except for the age and intensity of dynamic pain before surgery; 10 patients could not be contacted. Patients with and without CPS had statistically significant differences in 8 variables: the gender, age, intensity of dynamic pain before surgery and on the 1st postoperative day, expectation of postoperative pain, SA, PA, and depression level (Table 4).

Table 4. Characterization of patients with and without chronic pain syndrome 5—7 months after surgery

**Table 4.** Characterization of patients with and without chronic pain syndrome 5—7 months after surgery

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The gender, pain threshold (assessed by pressure algometry), intensity of dynamic pain before surgery, and expectation of postoperative pain are the risk factors for severe acute postoperative pain in spine surgery. A statistically significant multinomial logit regression model that includes these prognostic parameters enables predicting mild dynamic pain on the 1st postoperative day with an accuracy of 70%; 95% CI (63—76). The age and intensity of dynamic pain on the 1st postoperative day are the risk factors for chronic postoperative pain in spine surgery. A statistically significant multinomial logit regression model that includes these prognostic parameters enables predicting CPS 5—7 months after surgery with an accuracy of 65%; 95% CI (59—71). The developed software that is implemented as calculators in MS Excel evaluates the likelihood of mild acute dynamic pain on the 1st postoperative day and the likelihood of chronic pain syndrome 5—7 months after surgery for a particular patient before surgery.

Author contributions: 
The concept and design of the study — P.G. and V.T. 
Collection and processing of data — P.G., N.D., and A.E. 
Statistical processing — P.G. and O.R. 
Writing the text — P.G. 
Editing — V.T., A.G., and O.R.

Authors declare no conflict of interest.

REFERENCES

Conclusions

Table 5. Parameters of a multinomial logit regression model for calculating the likelihood of chronic pain syndrome 5—7 months after surgery (n=272)

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Regression coefficient β</th>
<th>Standard error</th>
<th>Wald criterion χ²</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age, years, Me (UQ; LQ)</td>
<td>0.02612</td>
<td>0.01</td>
<td>6.312</td>
<td>0.012</td>
</tr>
<tr>
<td>Motion pain on the 1st postoperative day (VAS), cm, Me (UQ; LQ)</td>
<td>0.12422</td>
<td>0.053</td>
<td>5.507</td>
<td>0.019</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.12981</td>
<td>0.535</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 6. Classification matrix of a logit regression model for predicting chronic pain syndrome 5—7 months after surgery

<table>
<thead>
<tr>
<th>Simulation results</th>
<th>Observed values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No CPS (n=30)</td>
<td>No CPS (n=99)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>CPS (n=173)</td>
<td>16</td>
</tr>
<tr>
<td>CPS (n=242)</td>
<td>No CPS (n=99)</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>CPS (n=173)</td>
<td>157</td>
</tr>
</tbody>
</table>

P=1/(1+e−Y),
where: Y=−1.129 + 0.026×A + 0.124×MP,
A is the age, and MP is motion pain on the 1st postoperative day.

Correspondingly, the likelihood of CPS absence is 1−P. This model was implemented as a calculator in MS Excel. The model quality was good (the Hosmer-Lemeshov criterion was 3.1; p=0.928). The classification matrix is shown in Table 6.

Point and interval estimates of the model performance indicators, which were calculated from the classification matrix, were as follows:

- DSp=14/(14+85)=14%; 95% CI (8—71);
- PPV=157/(157+16)=91%; 95% CI (85—99).

The model demonstrates statistically significant DSp (the model well identifies patients who will have CPS at 5—7 months after surgery among all patients with CPS) and PPV (if CPS is predicted, it will highly likely occur). Indicators of predictive value are more important for practical application of the model; therefore, PPV should be considered as the main result.

The developed software that is implemented as calculators in MS Excel evaluates the likelihood of mild acute dynamic pain on the 1st postoperative day and the likelihood of chronic pain syndrome 5—7 months after surgery for a particular patient before surgery.

Author contributions: 
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Collection and processing of data — P.G., N.D., and A.E. 
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Writing the text — P.G. 
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Authors declare no conflict of interest.

REFERENCES

Received: 17.08.17
The article is devoted to the actual topic — investigation of pain in patients after surgical treatment for degenerative diseases. The authors focused on predicting the development of postoperative pain syndrome. The task of predicting the development of pain is topical. Expectation of pain syndrome may influence the treatment approach. The authors have solved the problem of predicting pain after spine surgery. The prognostic model is based on a logistic regression of data from 291 patients. The study results indicate that the model quality can be limited to a small set of data (limited sample size) and the use of standard statistical software. Widespread practical application of the findings requires further research, data collection, use of other prognostic models, evaluation of their accuracy, and comparison of them with each other. Obviously, this study can be considered as one of the stages of a large study aimed at searching for optimal prognostic models.

A.G. Nazarenko (Moscow, Russia)

Commentaries

This study is devoted to the actual topic — predicting acute and chronic pain after spinal neurosurgery. It is no secret that pain is recognized as the main complaint of patients with spinal pathology because of which they consult the neurosurgeon. And it is actually annoying when neurosurgical intervention does not resolve this problem or even leads to chronic pain. This issue is addressed in the extensive literature dealing with various aspects of pain. The authors focused on predicting the severity of acute postoperative pain and its chronicization. In 291 patients with various spinal pathologies and different anesthetic treatments, by using a complex mathematical apparatus and laborious research methods, the authors achieved their goal — they identified the most reliable predictors for intensity of acute postoperative pain and its chronicization. Undisputed achievement of the authors is the development of special calculators based on the predictors. But here, I have some doubts. First, a calculator providing an accuracy of 70% will hardly be interesting to anybody. Second, the phenomenon of acute postoperative pain and its subsequent chronicization is a very complex, personalized, and multicomponent process, and, in practice, it would probably be more reasonable to rely on the very phenomenon of pain.

Thus, this article is based on the authors’ great work and provides interesting facts that may be important for spinal neurosurgeons, algologists, and radiologists.

A.Yu. Lubnin (Moscow, Russia)
Surgery of posterior cranial fossa tumors in children in the prone position. The surgical technique features

YU.V. KUSHEL', V.S. SOROKIN, B.Z. CHEL’DIEV*, A.R. TEKOEV

Burdenko Neurosurgical Institute, 4-ya Tverskaya-Yamskaya Str., 16, Moscow, Russia, 125047

Posterior cranial fossa tumors are the most common neuro-oncological pathology of childhood. More than half of them are located along the midline, occupying the cerebellar vermis and 4th ventricle cavity. Historically, most of these tumors were operated on with the patient in sitting position. This tendency has significantly changed in the last 30 years. For example, 95% of all operations in Japan are now performed with the patient in lying position; for the US and Europe, these figures are 80 and 60%, respectively. This global tendency of switching to the lying position is mainly associated with a high risk of venous air embolism in the sitting position. In the period between 1999 and 2013, the first author used only the sitting position for resection of PCF tumors. During this period, he performed 606 operations. In patients with large/giant tumors (usually, these were piloid astrocytomas with cysts), the surgeon often faced the problem of excessive retraction of the cerebellum and rupture of the bridging veins, sometimes outside the surgical approach area. This situation led either to massive blood loss or to venous air embolism.

Material and methods. Therefore, beginning at 2013, we started to selectively use the prone position in cases of hemispheric piloid astrocytomas of the cerebellum. This initial experience allowed us to assess the surgical features of the procedure and use the experience in more complex interventions. Since the middle of 2016, given the tendency of using key-hole approaches, we have increasingly used the prone position for various tumors of the 4th ventricle. Between November 2016 and September 2017, the first author performed 113 surgeries for PCF tumors in children; of these, only 4 operations were performed in the sitting position. Thus, in less than a year, the prone position has become the main one in surgery for all PCF tumors in our practice.

In this article, we would like to share our practical suggestions both about using the prone position and about its advantages and disadvantages that should be considered by a doctor who does not have experience of PCF surgery with the patient in prone position.

Keywords: posterior cranial fossa tumors, prone position surgery.

Abbreviations:
VAE — venous air embolism
EVD — external ventricular drain
DM — dura mater
PCF — posterior cranial fossa

Our decision to selectively use the lying position was dictated not only by this reason. In the period between 1999 and 2013, the first author used only the sitting position for resection of PCF tumors. During this period, 606 operations were performed. In patients with large/giant tumors (usually cystic piloid astrocytoma), the surgeon often faced the problem of excessive cerebellar retraction and rupture the bridging veins, sometimes outside the surgical approach area. This situation led either to massive blood loss or to VAE, which caused considerable stress in both a patient and a surgical team, increasing the time of surgery and, in some cases, leading to a persistent neurological deficit. Therefore, since 2013, we have selectively used the lying position in hemispheric piloid astrocytomas of the cerebellum. This initial experience allowed us to assess surgical aspects of the unusual position and features of equipment and personnel arrangement during surgery, understand potential limi-
tions and difficulties, and assure ourselves of the possibility of more complex surgery. Since mid-2016, given a trend of using keyhole approaches, we have extensively used the prone position in surgery of small PCF tumors; sometimes, medium-sized tumors were resected even through a burr hole (Fig. 1). Since the end of 2016, we have begun to routinely use the prone position in surgery for fourth ventricle tumors. From November 2016 to September 2017, the first author of this article performed 113 interventions in children with PCF tumors, with only 4 operations being performed in the sitting position. Therefore, the prone position has become, in less than a year, the main position in surgery for all PCF tumors in the first author’s practice. In this article, we would like to share our practical considerations about both using the prone position and the advantages and disadvantages associated with the position.

A general concept of fourth ventricle tumor resection in the prone position

Features of patient preparation

From a surgical point of view, there is no need in any special preparation of the patient. The important anesthesia aspect is the need to remember, when installing

Fig. 1. An example of the use of a burr hole approach for resection of a medium-sized cerebellar piloid astrocytoma in a patient in the lying position.

a — a tumor with a small cyst is seen on a preoperative contrast-enhanced T1-weighted MRI scan. The picture is typical of piloid astrocytoma; b — marking a skin incision; c — a 12 mm burr hole is made; d — final stage of tumor resection via the burr hole; e — general view of the wound after hemostasis; f — control contrast-enhanced T1-weighted MRI scan 2 months after surgery, which confirms complete tumor resection.

Fig. 2. Intubation and preparation of the patient’s face to prevent potential penetration of disinfectant to the eyes when processing the surgical site.

a — use of a reinforced tube avoids kinking problems; b — eye area is extensively covered with an incision-preventing tape to avoid potential penetration of disinfectant.
venous catheters for infusion of various fluids, that the upper part of the patient’s body will be completely inaccessible to the anesthesiologist after draping of the surgical field and arrangement of the surgical team around the patient. Orotracheal intubation is performed through a reinforced tube due to a risk of kinking of a standard tube, especially a small diameter tube. The use of a gastric tube is recommended in all cases due to a high risk of regurgitation (we use an orogastric tube that is removed in the operating room after surgery). A protective eye gel is put under the eyelids, and the entire face area is carefully covered with a sterile transparent tape (Fig. 2). When we started to use the prone position in surgery of the PCF, there were 2 cases of chemical keratitis due to penetration of an agent for surgical site treatment to the eyes taped according to the conventional technique. The explanation was very simple: in the prone position, the lateral eye corner area is one of the lowest facial points where a disinfectant drains during treatment of the surgical site. The use of a urinary catheter is desirable even in planning of very short interventions because its placement during surgery, if necessary, will be problematic.

Surgery planning features
The surgeon operates on one or two sides of the patient, being in line with the patient’s shoulders. The main

Fig. 3. Schematic illustration of the microscope angle of view relative to the fourth ventricle floor.
The red dashed line denotes the angle relative to the fourth ventricle floor, which is usually used for manipulations in the wound, with the patient being correctly positioned on the operating table.

Fig. 4. Intraoperative image of the ostium of the Sylvian aqueduct after resection of a medulloblastoma of the cerebellar vermis and fourth ventricle.
a — margin of the skin wound; b — fourth ventricle floor (rhomboid fossa); c — distal ostium of the Sylvian aqueduct.

Fig. 5. The patient’s position on the operating table for resection of a fourth ventricle tumor.
The inset at the top shows a projection of brain structures.

Fig. 6. Schematic demonstrating arrangement of personnel during surgery.
1 — surgeon; 2 — assistant; 3 — surgical nurse; 4 — anesthesiologist; 5 — anesthesiologist assistant; A — anesthesia console with an anesthesia apparatus; M — microscope; S — surgical console with all equipment.
Our initial concerns were associated with the access to the most rostral tumor parts — in the cerebral aqueduct and superior medullary velum region. Both the surgical experience and the analysis of MRI data with geometric reconstruction of attack angles completely dispelled this prejudice (Fig. 4). The ipsilateral posterolateral tumor pole causes the greatest problems. Approximately in 1/3 of cases, positions of the surgeon and the microscope have to be changed, and it is necessary to be ready to operate on both sides of the patient. To make manipulations maximally convenient, the patient’s head should be bent in such a way to bring the plane of the fourth ventricle floor to the vertical plane as close as possible. In this case, there are no problems with the rostrocaudal access to tumor poles (Fig. 5). A skin incision is approximately 1/3, sometimes even 1/2, as short as a similar incision in the sitting position. On average, a 5 cm incision is sufficient. Unlike the sitting position, inferior extension of the incision does not improve accessibility of the rostral fourth ventricle. At present, we plan the lower incision margin at the level of the upper edge of the C1 vertebra or even foramen magnum edge in the case of a wide C0—C1 gap (in some cases, we resected a fourth ventricle tumor through an anatomically wide C0—C1 gap, which could not be done in the sitting position). The surgeon should pay more attention to lateral access to the tumor, which dictates the size of craniotomy. Regardless of hydrocephalus severity, we have not used an external ventricular drain (EVD) intraoperatively (in the sitting position, the EVD have been implanted in all patients with hydrocephalus immediately after the anesthetic stage).

Features of personnel and equipment arrangement

We have adapted the arrangement of equipment with allowance for the fact that devices, such as an anesthesia apparatus, floor stands for devices, and a microscope, are actually stationary and can only be moved within small limits (Fig. 6). This approach to solving the habituation problem of surgical personnel demonstrated a high efficiency. Actually all of them, except for the surgeon, continued to work under the usual conditions. In addition, the proposed arrangement allows the surgeon to quickly and easily change the side of operation, if necessary.

Manipulation features

Soft tissue manipulations and craniotomy differ little from those in the sitting position. In the case of prolonged severe hydrocephalus, there is a risk of pronounced venous bleeding from emissaries (controlled with wax). In most cases, opening of the DM does not require a classical Y-shaped incision, a V-shaped incision to the atlanto-occipital membrane level is sufficient. In the case of pronounced occipital and/or marginal sinuses, the DM should be incised as quickly and completely as possible, after which bleeding is controlled by clamping and suturing of the sinus with locking stitches. Attempts of hemostasis (clipping, coagulation, etc.) upon partial opening of the DM are the most ineffective manipulations. After opening of the DM, it is sutured to soft tissues inside the surgical wound, but not retracted outwards using stay sutures. This technique enables more effective separation of the DM edges and provides wide angles of attack, which is particularly important in the case of a reduced skin incision. Due to slightly increased bleeding of tissues and draining of all liquids into the surgical area, the bone cut edges are surrounded with cotton pledgets. Then, the arachnoid membrane of the cisterna magna is opened, the spinal subarachnoid space is packed with cotton pledgets, and the stage of tumor resection through the foramen of Magendie begins. In the case of an expanded foramen of Magendie, the telovelar approach or dissection of the inferior medullary velum of the fourth ventricle can be used. The patient’s position excludes the use of spatulas (furthermore, they will likely put obstacles by occupying the wound space). We have applied a “dynamic retraction” technique when one of the tools in the

Fig. 7. Amount of intracranial air on the first postoperative day, depending on the patient's position on the operating table.

a — CT scan of a patient who underwent resection of a medulloblastoma of the cerebellar vermis and fourth ventricle in the sitting position. Of particular importance is pronounced pneumocephalus and smooth and compressed subarachnoid spaces, despite the presence of a functioning EVD placed at the beginning of surgery; b — CT scans of the patient after resection of the medulloblastoma of the cerebellar vermis and fourth ventricle in the lying position. There is a minimal amount of intracranial air, good relaxation of the ventricular system, and wide subarachnoid spaces. It should be noted that we do not use a perioperative EVD in the prone position, regardless of hydrocephalus severity.
surgeon hands is alternately used as a retractor. The first stage, internal decompression, is performed in the “top-down” direction; its purpose is to reach the area of usually dilated rostral portions of the fourth ventricle (the aqueduct ostium area). The aqueduct ostium is immediately packed with a pledget to prevent leakage of blood into the ventricular system. If the patient is correctly positioned, and the fourth ventricle floor is located vertically, the risk of injury to the brainstem is minimal; although at the beginning of resection, there is no such a good anatomical orientation as that in the sitting position. After reaching the rostral portions of the fourth ventricle, the orientation in the wound and the tumor/brainstem relationship become clear, and further tumor resection differs little from that in the sitting position. The biggest disadvantage is impossibility of effective work without suction. At the beginning of surgery, the wound is constantly filled with cerebrospinal fluid and blood, which requires active aspiration. As the tumor is resected, bleeding and the amount of CSF decrease, and manipulations become more comfortable. As the tumor is resected, the wound walls tend to smooth out (we work without retractors). To keep the wound walls in a position convenient for manipulations, cotton pledgets should be used, which are put into the resected tumor bed and enableatraumatic manipulations of the brain wound edges during surgery. The hemostasis stage is not associated with any features.

**Features of the early postoperative period**

According to our experience, if patients are in a satisfactory preoperative status, there are no signs of intraoperative brainstem infiltration and significant deviations during anesthesia, patients operated on in the lying position can be transferred to a general ward after awakening. According to our subjective estimates, the level of their activity and wakefulness in the first few days is higher than that in similar patients operated on in the sitting position. The main explanation for this phenomenon may be a smaller degree of pneumocephalus and, in particular, a smaller amount of air in the ventricular system (Fig. 7). Perhaps, some contribution to early activation is made both by the lack of an EVD and by a smaller amount of soft tissue dissection (less pronounced pain syndrome). Some patients were discharged in a good condition 2 to 3 days after surgery. There was no similar early discharge in patients operated on in the sitting position.

**Authors declare no conflict of interest.**

**REFERENCES**


**Commentary**

The use of modern neurosurgical technologies has led to the fact that indicators, such as postoperative lethality and perioperative complications, are reduced to very low levels in leading specialized clinics. From an oncological point of view, differentiated approaches to combined treatment enable achieving long-term remission or even complete recovery of children with this pathology in some cases. In general, it should be noted that the results of treatment of posterior cranial fossa tumors have become not so deplorable over the past few decades.

In the existing paradigm, even small and rare surgical complications have a tragic connotation. A further reduction of the risks of surgical complications is, of course, an actual applied problem. Perioperative problems associated with positioning of the patient on the operating table constitute a separate group of complications.

In general, the requirements for positioning of the surgical patient on the operating table include patient convenience, adequate maintenance of overall homeostasis (hemodynamics, oxygenation), prevention of joint injuries, damage to nerve trunks, and bedsores, a comfortable approach to the surgical field, and adequate use of surgical equipment (operating microscopes, endoscopes etc.). In these terms, the sitting position is one of the most dangerous ones in surgery in general and in neurosurgery in particular. First of all, it is air embolism, rupture of the bridging veins, and positional plexopathy. The latter is very resistant to treatment but, unlike the former, is not associated with life-threatening risks for the patient and does not.
lead to severe consequences. Therefore, the desire to avoid these problems by changing the patient’s position is quite clear.

In the publication “Surgery of posterior cranial fossa tumors in children in the prone position”, Yu.V. Kushel’ and co-authors in detail assess the advantages and disadvantages of the alternative to the sitting position. The article describes in detail not only features of the surgical technique for resection of posterior cranial fossa tumors in children but also important components of positioning, such as a venous approach, prevention of keratitis, and arrangement of medical equipment and personnel, which presents this publication as a description of the full surgical technique. The article, of course, is of interest to a large variety of neurosurgeons working in the area of interest and may serve as an example of a meticulous and thoughtful analysis of “simple” (only at a first, uninitiated glance) surgical problems.

As for own experience in surgery for posterior cranial fossa tumors in general and in children in particular, the position on the operating table is chosen individually, depending on the age, body type, concomitant diseases, and anatomical variant of the neoplasm location during preoperative planning, based on assessment of risks of potential complications.

In conclusion, I want to congratulate the authors with another elegant and useful publication.

D.A. Gulyaev (St. Petersburg, Russia)
Preoperative and Postoperative Ophthalmic Symptoms in Patients With Space-occupying Lesions of the Midbrain and Pineal Region


Burdenko Neurosurgical Institute, 4-ya Tverskaya-Yamskaya Str., 16, Moscow, Russia, 125047

The most common clinical manifestations of space-occupying lesions of the midbrain and pineal region are oculomotor and pupil disorders and ophthalmoscopic signs of intracranial hypertension.

**Purpose** — to identify patterns of neuro-ophthalmic symptoms before and after surgical treatment in patients with space-occupying lesions of the midbrain and pineal region.

**Material and methods.** We analyzed neurological symptoms in 231 patients with space-occupying lesions of the midbrain and pineal region before and after surgical treatment. Malignant tumors were detected in 121 patients; benign tumors were present in 73 patients; 37 patients were diagnosed with pineal gland cysts. Patients with suspicion of germinoma underwent tumor biopsy only; the other patients underwent tumor resection. Developed symptoms partially regressed in the long-term period, and finally, only 29% of patients had deterioration of oculomotor and pupillary functions compared to the preoperative level.

**Results and discussion.** Before surgery, oculomotor and pupil disorders were detected in more than half of the (67%) patients; ophthalmoscopic signs of intracranial hypertension were present in 38% of the patients. Neuro-ophthalmic symptoms significantly more often occurred in patients with malignant tumors. Midbrain symptoms were significantly more pronounced in germ cell tumors than in other malignant neoplasms. In the early postoperative period after tumor resection, deterioration of oculomotor and pupillary functions occurred in 46% of cases; there were no changes in 51% of cases; improvement occurred in 3% of cases. After tumor biopsy, symptoms in all patients with germinomas remained at the preoperative level. Developed symptoms partially regressed in the long-term period, and finally, only 29% of patients had deterioration of oculomotor and pupillary functions compared to the preoperative level.

**Keywords:** midbrain, pineal region, surgery, oculomotor and pupil disorders.

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Space-occupying lesions of the midbrain and pineal region are deep-seated neoplasms, which vary in histological structure but share similar clinical manifestations. Midbrain and pineal region tumors are a rare type of pathology. For instance, pineal region tumors comprise 0.4—1% and 3—8% of all brain tumors in adults and children, respectively [1—4]. Midbrain tumors constitute 1—2% of all brain tumors in children and are even more rare in adults [5]. Pineal cysts are diagnosed in 1.1—4.3% of the adult population. They are often accidentally diagnosed during brain MRI or CT [6].

Neuro-ophthalmic symptoms are the key symptoms in patients with tumors of this localization, they are manifested by the development of papilledema (PE), oculomotor and pupil disorders, which determines the significance of ophthalmological examination in these patients. According to modern literature, no detailed analysis of the relationship between neuro-ophthalmic symptoms and neoplasm histology has been ever conducted. Data changes in symptoms after treatment of such patients are also sparse [7—10]. Deterioration of the midbrain symptoms, which often occur after tumor resection, adversely affects the quality of life of patients. There is a belief that oculomotor and pupil disorders regress after resection of the space-occupying lesions of the midbrain and pineal region [8]. However, other authors [7, 10] present evidence that the disorders developed after surgery remain for a long period of time.

**Results and discussion.** Before surgery, oculomotor and pupil disorders were detected in more than half of the (67%) patients; ophthalmoscopic signs of intracranial hypertension were present in 38% of the patients. Neuro-ophthalmic symptoms significantly more often occurred in patients with malignant tumors. Midbrain symptoms were significantly more pronounced in germ cell tumors than in other malignant neoplasms. In the early postoperative period after tumor resection, deterioration of oculomotor and pupillary functions occurred in 46% of cases; there were no changes in 51% of cases; improvement occurred in 3% of cases. After tumor biopsy, symptoms in all patients with germinomas remained at the preoperative level. Developed symptoms partially regressed in the long-term period, and finally, only 29% of patients had deterioration of oculomotor and pupillary functions compared to the preoperative level.

**Keywords:** midbrain, pineal region, surgery, oculomotor and pupil disorders.

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The aim of the study is to identify patterns of neuro-ophthalmic symptoms before and after surgical treatment in patients with various types of space-occupying lesions of the midbrain and pineal region.

**Material and methods**

A total of 231 patients with space-occupying lesions of the midbrain (28) and pineal region (203), who underwent treatment at Burdenko Neurosurgical Institute in 2005 to 2015, have been examined. Age of the patients ranged from 2 to 67 years (mean age, 24 years); there were 62 children, 108 men and 123 women. Space-occupying neoplasms were resected in 144 patients with midbrain and pineal tumors and all of 37 patients with a pineal cyst. The following surgical approaches were used: supracerebellar (91 cases), occipital tentorial (66), transcallosal (9), trans-fourth ventricle (5), subtemporal (4), and other approaches (6). Patients with suspicion of pineal germinoma underwent open biopsy (26) or stereotactic biopsy (24) of the tumor. Completeness of tumor resection was evaluated using surgical protocols, brain CT and MRI data. Total and subtotal tumor resection was performed in 111 patients, 33 patients underwent partial tumor resection. A total of 42 patients underwent cerebrospinal fluid shunt placement for normalization of intracranial pressure prior to admission. Pathomorphological verification of space-occupying le-
sions was performed in all patients (Table 1). Benign tumors were diagnosed in 73 patients, malignant tumors were present in 121 patients. All patients underwent MRI or CT and neurologic examination before and after surgery.

All patients were examined by a neuro-ophthalmologist before surgery and in the early postoperative period. A total of 89 patients were examined in the long-term period from 1.5 months to 8 years (median, 21.5 months). In addition to assessment of visual acuity, field of vision, and ophthalmoscopy, special attention was paid to oculomotor and pupillary function during neuro-ophthalmic examination. Evaluation of visual disturbances was carried out according to the classification developed by us, with the score ranging from 0 to 6. Gaze and movement of the each eye were evaluated separately. Absence of deterioration was given a score of 0 points, while 6 points were considered as the absence of arbitrary and reflex gaze (Table 2). Pupillary disorders were assessed using a scale of 0 to 2: normal light reflex was given a score of 0 points, reduced pupillary light reflex was scored 1 point, and lack of light reflex equated 2 points. Depending on the severity of oculomotor and pupillary disorders, groups of patients with early-stage, moderate and severe impairments were identified (Table 3).

Changes in the oculomotor and pupillary functions were evaluated in accordance with the developed scoring system. In addition, the severity of n. oculomotorius lesion was also taken into account.

To objectivize oculomotor disorders and their changes, a VF5 video oculography equipment consisting of a combined mask, two infrared cameras, software, and a database was used.

Data analysis was carried out using R software environment for statistical computing (www.r-project.org). For statistical comparison of the group parameters, $\chi^2$ and Fisher’s exact test were used. Differences were considered significant at $p<0.05$.

Results and discussion

Neuro-ophthalmic symptoms before surgery. A total of 231 patients were examined in the preoperative period. Most often, patients complained of double vision and headache. The leading ophthalmologic symptoms were oculomotor and pupillary disorders, which were diagnosed in 154 (67%) patients. The majority of patients 94 (41%) had early-stage symptoms, 22 (10%) patients exhibited moderate symptoms, and 38 (16%) patients had severe symptoms. Pupillary light reflex disorders were most frequently observed (139 (60%) patients), which manifested through moderate pupil dilation and reduced pupillary light reflex. Symptoms of the nucleus lesion of the third pair of cranial nerves (CN) was observed in 1 patient, 3 patients had unilateral lesion of n. oculomotorius at the level of the root.

Comparison of the symptoms among patients with midbrain and pineal tumors revealed no significant differences in the incidence and severity of midbrain symptoms ($p>0.05$) (Table 4).

The severity of oculomotor and pupil disorders depending on the histological diagnosis is presented in Table 5. Analysis showed that midbrain symptoms were significantly more frequent in patients with germ cell tumors ($p<0.05$). More than half of the patients of this group had moderate and severe disorders.

There were no significant differences in the incidence and severity of midbrain symptoms in patients with astrocytic tumors of the midbrain, ependymomas and tumors of the pineal gland parenchyma ($p>0.05$).

Neuro-ophthalmic symptoms were rare in patients with meningiomas of the pineal region ($p<0.05$) and manifested primarily as pupil disorders.

This symptom was even rarer in the group of patients with pineal cyst. This is quite expected considering the nature of growth and the anatomical and topographic location of these lesions.

Assessment of the relationship between incidence and severity of oculomotor and pupil disorders with the degree of tumor malignancy showed that these disorders were more frequent and more pronounced in patients with malignant tumors (105 (87%) cases) than benign lesions (43 (59%) cases), ($p<0.05$). From our point of view, this is due to the infiltrative nature of tumor growth. It should be noted that oculomotor and pupil disorders were significantly more pronounced in patients with germ cell tumors than in patients with other types of malignant tumors ($p<0.05$).

Ophthalmoscopic signs of intracranial hypertension (ICH) in the form of PE or secondary post-PE atrophy were diagnosed in 87 (38%) patients. Fundus signs of ICH were significantly more frequent in patients with malignant tumors ($p<0.05$). There were no PE cases among patients with a pineal cyst. Midbrain symptoms were significantly more frequent ($p<0.05$) in patients with ophthalmoscopic signs of ICH (75 (86%) patients) as well as in patients with MRI-detected occlusive hydrocephalus (77 (73%) cases). This allows us to suggest that ICH contributes to the development of the midbrain symptoms, in particular, in the development of pupil disorders due to the impact on the posterior regions of the third ventricle and the pretectal region. Exceptions were patients with germinomas, with the vast majority of them having oculomotor and pupil disorders regardless of the presence or absence of ICH signs.

The study showed that visual functions were normal for the most of patients (206 (89%) cases). Reduced visual acuity in 25 patients and changes the field of vision in 14 patients were due to PE or secondary atrophy of the optic nerves.

Neuro-ophthalmic symptoms after tumor resection. A total of 231 patients were examined in the early postoperative period. Changes in the oculomotor and pupillary
Table 1. Pathomorphological examination data in patients with space-occupying lesions of the midbrain and pineal region

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytic tumors</strong></td>
<td></td>
</tr>
<tr>
<td>piloid astrocytoma</td>
<td>30</td>
</tr>
<tr>
<td>anaplastic astrocytoma</td>
<td>3</td>
</tr>
<tr>
<td>diffuse astrocytoma</td>
<td>2</td>
</tr>
<tr>
<td>glioblastoma</td>
<td>8</td>
</tr>
<tr>
<td>glial tumor (unspecified degree of malignancy)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Ependymal tumors</strong></td>
<td></td>
</tr>
<tr>
<td>ependymoma</td>
<td>7</td>
</tr>
<tr>
<td>anaplastic ependymoma</td>
<td>6</td>
</tr>
<tr>
<td><strong>Tumors of the pineal gland parenchyma</strong></td>
<td></td>
</tr>
<tr>
<td>pineocytoma</td>
<td>11</td>
</tr>
<tr>
<td>pineocytoma-pineoblastoma</td>
<td>18</td>
</tr>
<tr>
<td>pineoblastoma</td>
<td>28</td>
</tr>
<tr>
<td>papillary tumor of the pineal region</td>
<td>6</td>
</tr>
<tr>
<td><strong>Germ cell tumors</strong></td>
<td></td>
</tr>
<tr>
<td>germinoma</td>
<td>50</td>
</tr>
<tr>
<td>teratoma</td>
<td>7</td>
</tr>
<tr>
<td>mixed tumors</td>
<td>2</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>meningioma</td>
<td>15</td>
</tr>
<tr>
<td>pineal cyst</td>
<td>37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>231</td>
</tr>
</tbody>
</table>

Table 2. Score evaluation of oculomotor disorders

<table>
<thead>
<tr>
<th>Score, points</th>
<th>Gaze</th>
<th>Eye movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Healthy</td>
<td>Healthy</td>
</tr>
<tr>
<td>1</td>
<td>1 mm limitation</td>
<td>1 mm limitation</td>
</tr>
<tr>
<td>2</td>
<td>1/3, limitation of normal value</td>
<td>1/3, limitation of normal value</td>
</tr>
<tr>
<td>3</td>
<td>1/3, limitation of normal value</td>
<td>1/3, limitation of normal value</td>
</tr>
<tr>
<td>4</td>
<td>1/3, limitation of normal value</td>
<td>1/3, limitation of normal value</td>
</tr>
<tr>
<td>5</td>
<td>No arbitrary gaze</td>
<td>No movements</td>
</tr>
<tr>
<td>6</td>
<td>No reflex gaze</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 3. Scoring of the severity of oculomotor and pupil disorders

<table>
<thead>
<tr>
<th>Disorder stage</th>
<th>Pupillary light reflex</th>
<th>Vertical gaze</th>
<th>Interpupillary distance deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-stage</td>
<td>1 point/2 points</td>
<td>Normal value or 1 point limitation of the upward gaze</td>
<td>Normal value or slight deviation</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 point/2 points</td>
<td>2–3 points limitation of the upward/downward gaze</td>
<td>Normal value or slight deviation</td>
</tr>
<tr>
<td>Severe</td>
<td>2 points</td>
<td>4–6 points limitation of the upward/downward gaze</td>
<td>Normal value or deviation of various severity</td>
</tr>
</tbody>
</table>

function were absent in 50 patients with germinomas who received tumor biopsy only and in half of the patients (92 (51%) cases) who underwent tumor resection.

Deterioration of oculomotor function occurred in approximately half of patients (83 (46%) cases). The symptom mainly increased to the degree of moderate or severe impairments and was manifested primarily by impaired vertical gaze and light reflex. Two patients developed third CN nucleus lesion, and one patient had unilateral lesion of n. oculomotorius at the level of the root. It is worth mentioning that pronounced hemoptysis, which appeared after surgery in patients with nucleus lesion of the oculomotor nerve, partially regressed by the time of discharge.

Deteriorations more often occurred after total and subtotal tumor resection (53% of patients) than after partial resection (36% of patients). However, we did not obtain a significant difference (p>0.05).
Table 4. Incidence and severity of oculomotor and pupil disorders in patients with lesions of the midbrain and pineal region

<table>
<thead>
<tr>
<th>Oculomotor/pupil disorders</th>
<th>Number of patients with midbrain tumors, %</th>
<th>Number of patients with pineal tumors, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>7 (25)</td>
<td>38 (23)</td>
</tr>
<tr>
<td>Early stage</td>
<td>14 (50)</td>
<td>75 (45)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (7)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (18)</td>
<td>33 (20)</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>166</td>
</tr>
</tbody>
</table>

Table 5. Incidence and severity of oculomotor and pupil disorders depending on the histological structure of the space-occupying lesion

<table>
<thead>
<tr>
<th>Histological structure</th>
<th>Healthy, abs. (%)</th>
<th>Early stage, abs. (%)</th>
<th>Moderate stage, abs. (%)</th>
<th>Severe stage, abs. (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumors</td>
<td>4 (7)</td>
<td>17 (29)</td>
<td>19 (32)</td>
<td>19 (32)</td>
<td>59</td>
</tr>
<tr>
<td>Tumors of the pineal gland parenchyma</td>
<td>17 (27)</td>
<td>37 (59)</td>
<td>3 (5)</td>
<td>6 (9)</td>
<td>63</td>
</tr>
<tr>
<td>Astrocytic tumors</td>
<td>12 (27)</td>
<td>23 (52)</td>
<td>2 (5)</td>
<td>7 (16)</td>
<td>44</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>3 (23)</td>
<td>8 (62)</td>
<td>—</td>
<td>2 (15)</td>
<td>13</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>10 (67)</td>
<td>5 (33)</td>
<td>—</td>
<td>—</td>
<td>15</td>
</tr>
<tr>
<td>Pineal cysts</td>
<td>32 (87)</td>
<td>5 (13)</td>
<td>—</td>
<td>—</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>95</td>
<td>24</td>
<td>34</td>
<td>231</td>
</tr>
</tbody>
</table>

Only 6 (3%) patients experienced improvement in oculomotor and pupillary functions. Having compared changes in oculomotor and pupillary functions between patients with midbrain tumors and patients with pineal tumors, we found no significant differences. There were also no changes in the changes in symptoms between patients with benign and patients with malignant tumors. At the same time, we noted that patients with ependymomas (62%), tumors of the pineal gland parenchyma (56%) and astrocytic tumors (45%) more often had deterioration in symptoms. Less severe changes were observed in 3 (33%) out of 9 patients with non-germ cell carcinomas, since most of them already had moderate and severe disorders before surgery.

Oculomotor and pupillary functions were preserved at the preoperative level in most patients with meningiomas of the pineal region and pineal cysts (67 and 68%, respectively), i.e. at normal level or with minimal impairments. Fourteen (21%) of 66 patients operated on via occipital transtentorial approach developed homonymous hemianopsia, which regressed completely or partially in 10 (71.4%) cases on day 7—10 after surgery. Partial or complete regression was noted in 30 (52%) cases out of 58 patients with PE in the early postoperative period.

A total of 89 patients were examined in the postoperative period from 1.5 months to 8 years (median, 21.5 months). Analysis showed that symptoms regressed in 33 (79%) out of 42 patients who suffered deterioration in the early postoperative period. Of these, oculomotor function was restored to the preoperative level in 17 patients, and only 16 patients had partial regression of the developed disorders. Our data coincide with the results obtained by J. Nazzaro et al. [8], who revealed the develop-
development of Parinaud’s syndrome immediately after tumor resection and further partial function restoration.

Deterioration of symptoms compared with the early postoperative period was noted in one patient, which was associated with the continued tumor growth.

Thus, 37 (42%) patients exhibited no symptoms in the long-term period, and 33 (37%) patients had early-stage symptoms (see figure). Comparison of oculomotor and pupillary functions in the long-term period with their preoperative state showed that symptoms did not change in 56 (63%) patients, increased in 26 (29%) patients, and 7 (8%) patients had deterioration. These are the patients with no deterioration after surgery.

We believe that deterioration developed immediately after resection of space-occupying lesions of the midbrain and pineal region is both due to the direct midbrain injury, in particular the pretectal region, posterior regions of the third ventricle, posterior commissure, and impaired blood circulation in this region. This assumption is supported by the fact that more severe disorders developed in patients after total/subtotal rather than partial tumor resection, as well as sufficiently high frequency rate of recovery or function improvement at a later stage. M. Hart et al. [7] also place emphasis on the vascular factor in deterioration of the symptoms after tumor resection, in particular venous circulation disorders at the level of the posterior regions of the third ventricle.

We did not reveal significant differences in the changes of the midbrain symptoms in the long-term period in patients with space-occupying lesions of different localization and histological structure.

As for the signs of ICH, complete regression of PE was noted in all patients of the long-term period.

Conclusions

The study revealed a rather high incidence of symptoms in patients with space-occupying lesions of the midbrain and pineal region in the form of oculomotor and pupill disorders. Early-stage disorders were observed more often. There were no differences in the incidence and severity of symptoms in patients with tumors of the midbrain and pineal region. At the same time, pronounced symptoms were more often observed in patients with malignant tumors.

Oculomotor and pupill disorders were more pronounced in patients with germ cell tumors of the pineal region than in other patients with malignant tumors. Midbrain symptoms were absent or minimal in patients with meningiomas of the pineal region and pineal cysts.

Comparison of the incidence of midbrain symptoms and ICH signs showed that oculomotor and pupillary disorders are significantly more frequent in patients with signs of occlusive hydrocephalus according to the MRI data and patients with ophthalmoscopic signs of ICH.

Oculomotor and pupillary functions deteriorate in almost half of the patients after tumor resection. It is mostly related to the upward gaze. At the same time, oculomotor disorders largely regress after tumor resection in the long-term period.

Authors declare no conflict of interest.

REFERENCES


Received: 10.04.17
The presented work is devoted to the study of neuro-ophthalmic symptoms in patients with midbrain and pineal tumors. Clinical study included 231 patients, with 28 cases diagnosed with midbrain tumors with the remaining patients diagnosed with pineal tumors. The authors showed that the severity of oculomotor and pupil disorders depends on the histological structure of the tumor, and postoperative deterioration of functions is associated with the completeness of neoplasm resection.

According to the obtained results, open or stereotactic biopsy of the tumor does not lead to a change in neuro-ophthalmic symptoms, which is easily explained by the slight effect on the midbrain structures during these surgical interventions. Similar data were obtained after surgical resection of pineal cysts (37 cases). The greatest changes in neuro-ophthalmic syndromes were observed after total (111 cases) and partial (33 cases) tumor resection, while impairment was observed in 46% of cases. Having investigated the neurological status of patients in the long-term postoperative period, the authors noted partial restoration of lost functions in the early postoperative period.

Design of the work corresponds to the purpose of the study, an adequate analysis of the revealed changes in oculomotor functions is conducted, and their correlation with pre- and postoperative MRI data was evaluated.

The summary presents main points of the study. The list of references includes important sources, including recent ones.

In conclusion, the work is of interest for neurosurgeons, ophthalmologists and neurologists.

Yu.A. Grigoryan (Moscow, Russia)

Commentary

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In conclusion, the work is of interest for neurosurgeons, ophthalmologists and neurologists.

Yu.A. Grigoryan (Moscow, Russia)
Ependymoma is a central nervous system tumor that grows from ependymal cells lining the cerebral ventricles, central canal of the spinal cord, and filum terminale. Regardless of the histological type of ependymomas, they rarely have exophytic growth. Because of an extremely low occurrence rate of this phenomenon, we present two clinical cases of patients with classical intramedullary ependymomas (Grade II) having an extramedullary component.

**Material and methods.** The paper presents two clinical cases of patients with intramedullary-extramedullary ependymomas of the spinal cord. The surgical technique is described. After surgical treatment, the performance status of patients remained unchanged.

**Conclusion.** Radical removal of complex ependymomas provides conditions for long-term disease-free survival and further neurological recovery.

**Keywords:** intramedullary tumor, intramedullary-extramedullary tumor, ependymoma.

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Ependymoma is a central nervous system tumor that grows from ependymal cells lining the cerebral ventricles, central canal of the spinal cord, and filum terminale. In adults, 75% of ependymomas affect the spinal cord, and only 25% of ependymomas affect the spinal cord. Most spinal ependymomas grow from the central canal ependyma and are located intramedullary. They account for about 60% of all intramedullary tumors. Histologically, most intramedullary ependymomas belong to cellular (classic) ependymomas and are Grade II tumors. No more than 5% of intramedullary ependymomas are anaplastic tumors (Grade III). In single cases, there are also tanycytic, papillary, and clear-cell ependymomas as well as subependymomas [1–4].

About 50% of ependymomas located in the spinal canal grow from the filum terminale. Usually, these are extramedullary tumors. In the lumbar spine, they have an intramedullary component only if the tumor invades the medullary cone. According to the histological pattern, filum terminale tumors are myxopapillary ependymomas and belong to Grade I tumors [1]. Actually, myxopapillary ependymoma is the only CNS tumor that grows from glial tissue and is typically located extramedullary. Other histological ependymoma types not associated with the filum terminale have exophytic growth very rarely [3]. Due to an extremely low occurrence of this phenomenon, we describe 2 clinical cases of patients with classical intramedullary ependymomas (Grade II) with an extramedullary component. This is the first description of this pathology in Russian language.

**Results**

We have generalized the experience with treatment of intramedullary spinal cord tumors in the Neurosurgical Department of the Clinic of Nervous Diseases of the Sechenov First Moscow State Medical University and in the Department of Spinal Neurosurgery of the Burdenko Neurosurgical Institute. In both clinics, more than 800 patients with intramedullary space-occupying spinal cord lesions were operated on for 15 years. In this case, only 4 patients had ependymoma with intramedullary-extramedullary growth; in 7 patients, the tumor had subpial spread.

Below, we provide a description of clinical cases.

**Case 1**

A 26-year-old male patient B. presented with complaints of pain and numbness in his left lower limb, which intensified at night, and weakness in the left foot. According to a medical history, the pain in the left lower limb developed about 2 years ago. Gradually, a feeling of numbness in the left foot and lower leg was developed. Two months before admission, the patient felt weakness in his lower limb but continued to move independently, without additional support.

He underwent outpatient contrast-enhanced MRI of the thoracic spine and spinal cord. An intramedullary tumor at the T11—T12 level was detected (Fig. 1).

The tumor had an irregular shape and intensively and unevenly accumulated a contrast agent. Polyr syringoymelia cysts were located above and below the lesion. An outgrowth of an irregular triangular shape was clearly
seen on the tumor surface on the left, which suggested extramedullary growth.

At admission, paresis of the left calf muscles (3 points) was revealed in the neurological status. Pain and temperature hypoesthesia of the left foot and lower leg and mild impairment of deep sensitivity in both lower limbs, without clear signs of sensitive ataxia, were revealed. The patient moved independently, without additional support, but claudication in the left lower limb was present. The patient had grade II (McCormick scale) functional status.

12.04.16, the patient underwent elective surgery — resection of the extramedullary-intramedullary tumor of the lumbar enlargement (Fig. 2).

Surgery was performed with the patient in the prone position. The patient underwent laminectomy of the T10—T12 vertebrae. The dura mater (DM) was opened by a midline linear incision. Upon exploration, the spinal cord appeared moderately inflated and displaced to the right. A dilated tortured posterior median vein was visualized on the posterior surface of the spinal cord. Tortuosity of small vessels was present. Lateral to the midline, there was a bean-shaped tumor node growing from the spinal cord in a projection of the DREZ area. The node color was identical to that of the spinal cord. The arachnoid membrane in the tumor node region was tightened; the node was 6×3×3 mm in size (Fig. 2a). The node was resected (Fig. 2b). After tumor node resection, an intramedullary tumor was visualized through the destroyed spinal cord site. Access to the tumor through the DREZ was not convenient due to a large intramedullary part of the lesion. The posterior median vein in the area between two large tributaries was coagulated above the tumor projection. Posterior median myelotomy of about 1.5 cm in length was performed. Tumor tissue of gray-red color was found at a depth of less than 1 mm. The tumor was clearly demarcated from the spinal cord. The dorsal and lateral tumor surfaces were separated from the posterior columns. The posterior columns were moved apart and fixed to the DM with two pial sutures (Fig. 2c-e). An intramedullary tumor of an irregular and slightly elongated shape was found and resected. The intramedullary nodal was about 12 mm in diameter. Appearingly, the tumor was ependymoma with intramedullary-extramedullary growth. After tumor resection, the spinal cord in the tumor bed area appeared as a 2 to 3 mm thin-walled hollow cylinder (Fig. 2f). The cavity communicated, through a tissue defect in the DREZ area, with the projection of the extramedullary node resected at the beginning of surgery. Therefore, the tumor had an intramedullary-extramedullary location and perforated the spinal cord through the DREZ projection on the left. The pia mater was sutured with interrupted stitches. The hole perforated in the spinal cord by tumor tissue was preserved. The arachnoid membrane was sutured with a continuous stitch (Fig. 3a, b). The DM was also sutured with a continuous stitch. The surgical wound was closed in layers.

Control MRI of the thoracic spine and spinal cord (13.04.16) revealed postoperative changes at the T10—T12 level. The tumor was completely resected. The posterior CSF space was preserved (Fig. 3c, d).

According to a histological examination, the morphological picture and immunophenotype of the tumor corresponded to WHO Grade II ependymoma with an increased (6 to 7%) Ki-67 index (Fig. 4). In the postoperative period, pain syndrome in the left lower limb completely regressed, and mild sensitive ataxia developed. The postoperative wound healed by primary tension. A follow-up examination at 3 months after surgery revealed a slight decrease in foot paresis. Clinical manifestations of sensitive ataxia regressed. The patient walked independently, without support. The patient condition was grade II on the McCormick scale.

Given total tumor resection, postoperative radiotherapy was refused, despite the increased Ki-67 index.
Case 2

A 28-year-old male patient G. presented with complaints of weakness in his upper limbs and unsteady gait.

According to a medical history, the patient developed numbness and weakness in his right upper limb 9 months ago and, later, unsteady gait. After 6 months, the patient experienced weakness in his left upper limb.

The neurological status at admission: there was paresis of the right upper limb (3 points) and the left upper limb (3.5 points). Paresis of the lower limbs was 4 points in the proximal muscles and 5 points in the distal muscles. Tendon reflexes from the upper and lower limbs were increased, D=S. Tone in the upper and lower limbs was spastically increased, D=S. There was sensitive ataxia. The patient moved independently, but preferred to use additional support because of instability. The patient condition was grade III on the McCormick scale.

MRI of the cervical spine revealed an intramedullary tumor located at the C1—C3 level, which intensively accumulated a contrast agent (Fig. 5a, b). Above the tumor, there was syringobulbia. Below the tumor, there was a syringomyelia cyst. The upper tumor pole was located below the McRae line; there was no tumor invasion into the medulla oblongata. The cisterna magna was absent due to expansion of the medulla oblongata and upper cervical spine segments. In the lower tumor pole, there was a small tumor cyst whose walls accumulated a contrast agent. Lesion boundaries at the lower tumor pole, along the dorsal surface, were uneven, which suggested an ex-
tramedullary component of the tumor rising above the dorsal spinal cord surface.

On 14.09.16, the patient underwent resection of the extramedullary-intramedullary tumor at the craniovertebral junction level.

A laminectomy of the C1—C3 vertebrae and resection of the lower occipital squama of 2.5×2.5 cm in size were performed through a median approach, with the patient being in the park-bench position on the left side under endotracheal anesthesia. The DM was opened using a Y-shaped incision with branching above the marginal sinus. The DM of upper portions of the dural sac was significantly thickened. The spinal cord and lower medulla oblongata were swollen. In the C1—C2 projection on the posterior surface of the spinal cord, there was an extramedullary node of an intramedullary tumor, which was of gray color, oval in shape, and about 3 to 4 mm in size. The node completely covered the dorsal spinal cord surface. Remnants of the posterior columns in the form of a thin whitish film remained mainly in the lateral portions were seen on the extramedullary fragment surface (Fig. 5c). The posterior column remnants were laterally displaced from the dorsal surface of the extramedullary portion of the tumor (Fig. 5d).

A posterior median myelotomy was performed inferior to the extramedullary part of the tumor, in the C3 projection. A small syrinx located below the tumor was evacuated. The cystically altered lower pole of the intramedullary part of the lesion was exposed and resected. The tumor was partially resected, including resection of the extramedullary fragment and lower portion of the intramedullary fragment (Fig. 5f — an unresected tumor is indicated by an arrow). After fixation of the posterior columns, the remaining tumor was resected, except for its upper pole adjacent to syringobulbia (Fig. 5g — an unresected fragment of the upper tumor pole before removal is indicated by an arrow). Attempt to resect the upper tumor pole was accompanied by the development of severe bradycardia, which required interruption of surgery for 30 min until pulse stabilization. After that, the upper tumor pole was resected, and drainage of syringobulbia was performed (Fig. 5h — the entrance to the cyst cavity is indicated by an arrow). After tumor resection, the spinal cord appeared as a thin-walled hollow cylinder; cerebrospinal fluid pulsation was observed. The DM was repaired using a fascia lata fragment. The surgical wound was sutured in layers.

According to a histological examination, the morphological picture corresponded to WHO Grade II ependymoma with the Ki-67 index being less than 5% (Fig. 6).

On 15.09.16, the patient underwent control contrast-enhanced MRI that revealed no signs of residual tumor. Syringomyelia cysts collapsed. There was no accumula-

Fig. 3. Case 1.

a, b — intraoperative microphotographs. Appearance of the posterior surface of the spinal cord after suturing the pia mater (a), b — after suturing the arachnoid membrane; c, d — control postoperative MRI study. See explanations in the text.

Fig. 4. Case 1.

Histological tumor specimen. Staining with hematoxylin and eosin. ×200.
Fig. 5. Case 2.
Intramedullary tumor at the C1—C3 level. a, b — preoperative contrast-enhanced T1-weighted MRI scans; a — sagittal projection; b — frontal projection. The tumor intensively accumulating a contrast agent is seen. The unevenness of the lower tumor pole is indicated by an arrow; c—h — tumor resection stages. Intraoperative microphotographs. See explanations in the text; i — postoperative contrast-enhanced T1-weighted MRI scan, sagittal projection.
tion of a contrast agent in a projection of the resected tumor bed (Fig. 5i).

After surgery, there was deterioration of sensitive ataxia and paresis in the hands (up to 2 points). The patient could not move independently for 3 weeks due to pronounced instability; then, he began to move with support. At one month after surgery, strength in the limbs returned to the preoperative level, and the patient began to move independently using a walking frame. Despite worsening of sensitive ataxia, which persisted for 3 months after surgery, the patient condition was grade III on the McCormick scale at that moment. Thus, despite worsening of neurological symptoms after surgery, the patient’s condition returned to the preoperative functional level 3 months after the intervention; he was completely independent of any assistance.

Fig. 6. Case 2.
Histological tumor specimen. Staining with hematoxylin and eosin. × 200.

Reports of extra- and intramedullary ependymomas in the literature

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<th>Gender</th>
<th>Level of lesion</th>
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<td>Mixed glioma (ependymoma-astrocytoma)</td>
<td>Marked regression of motor and sensitive disorders</td>
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</tr>
<tr>
<td>4</td>
<td>S. Hentschel et al., 2004 [5]</td>
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<td>5</td>
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<td>6</td>
<td>L. Orozco et al., 2011 [9]</td>
<td>61</td>
<td>M</td>
<td>T3—T11</td>
<td>Lower paraparesis (more pronounced on the left), urinary incontinence, decreased sensitivity starting from the T5 level</td>
<td>Total resection of an extramedullary component. Resection of an intramedullary component</td>
<td>Ependymoma (Grade II)</td>
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<td>7</td>
<td>B. Kim et al., 2013 [8]</td>
<td>48</td>
<td>F</td>
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<td>Pain and weakness in the lower limbs decreased. Pelvic disorders did not regress</td>
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<td>8</td>
<td>G. Cicero et al., 2015 [4]</td>
<td>57</td>
<td>F</td>
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<td>Total resection</td>
<td>Tanycytic ependymoma (Grade II), Ki-67 — 3 to 4%</td>
<td>Pronounced regression of paresis in the left lower limb, back pain reduction</td>
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Discussion

Spinal ependymoma with intra- and extramedullary growth was first described by T. Ishikawa et al. in 1988 [5—7]. To date, we found 8 clinical cases of intra- and extramedullary ependymoma in the available literature, which were not associated with the filum terminale (see Table).

In all cases, ependymoma grew from the spinal cord to the outside, following the least resistance path — through the DREZ or posterior longitudinal fissure [8—10]. In the literature [11], there is also a report of 23 cases of intradural extramedullary ependymomas not associated with the filum terminale, but none of them grew from the intrathecal space to the spinal cord. An analysis of the literature data did not reveal a correlation between the ependymoma grade and the rate of extramedullary tumor extension. In our cases, the tumor in one of the patients (Table) had a Ki-67 index of 6 to 7%, which may only be interpreted as a tendency to transition into an anaplastic form; in the second case (Table), Ki-67 was below 5%, which is a normal value for low grade tumors.

Currently, neurosurgeons strive for complete resection of intramedullary ependymomas, which is possible in more than 90% of cases. Among the described extra- and intramedullary ependymomas, total resection was performed in only 3 out of 9 cases. Clinical improvement was usually achieved by complete resection of an extra- medullary component compressing the spinal cord from the outside. However, we believe that the presence of an extramedullary component that can be resected relatively easily, without a serious risk of neurological deficit deterioration, should not lead to refusal of total tumor resec- tion, including its intramedullary portion. In both pre- sented cases, we performed total tumor resection. In our cases, ependymomas were predominantly located intra- medullary and well demarcated from the spinal cord tissue. In similar patients, we consider unreasonable to limit the amount of surgery to an extramedullary tumor component. Both patients presented in the article re- mained within their preoperative functional status 3 months after surgery. Complete resection provided conditions for a long and disease-free period of life and further neurologic recovery that may last at least six months after resection of intramedullary tumors.

Authors declare no conflict of interest.

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Commentary

The article presents two clinical cases and a literature re- view devoted to rare cases of intra- and extramedullary ependy- momas. These cases should indeed be considered exquisite, although we have a similar case in our practice. Despite the limited number of reported cases, ependymomas with intra- and extramedullary growth are known to occur predominantly in young males (25—40 years). On the basis of the described clinical cases and our own experience, we may say that similar le- sions are always on the border between benign and anaplastic neoplasms — Grade II—Grade III. In particular, we observed transformation of anaplasia to tumor with subsequent rapid re- currence — postoperative one-year follow-up revealed no con- tinued growth, but a neoplasm with pronounced compression of the spinal cord rapidly developed in the following 3 months, which required urgent surgery.

The regularities described in the article in the form of Ki-67 values are indicative of initial propensity of intra- and extra- medullary ependymomas to anaplasia, which requires correc- tion of postoperative management with possible radiotherapy. This work is useful and stands out from the publications on rare neurosurgical pathologies.

A.O. Gushchina (Moscow, Russia)
Hemostatic disorders always bear a serious risk for neurosurgical patients, especially those with intracranial pathology [1—3]. These disorders can exist preoperatively or develop during surgery or in the postoperative period. Preoperatively diagnosed hemostasis disorders are apparently the most favorable situation, since it is possible to prepare and inject the missing hemostatic factors before planned neurosurgical intervention, when necessary [4]. The diagnosis of von Willebrand disease was established only after special hematology tests and only after surgery. Despite the use of specific therapy, the patient died due to intracranial hemorrhagic complications in the postoperative period. The paper discusses the problem of preoperative diagnosis of asymptomatic hemostasis disorders in neurosurgical patients and potential ways of its solution.

Keywords: hemostasis disorders, von Willebrand disease, neurosurgery, postoperative hematomas.

Abbreviations:
APTT — activated partial thromboplastin time
BMI — body mass index
CT — computed tomography
INR — international normalized ratio (laboratory coagulation test)
MRI — magnetic resonance imaging
FFP — freshly frozen plasma
DM — dura mater
TEG — thromboelastography
CNS — central nervous system

Hemostatic disorders always bear a serious risk for neurosurgical patients, especially those with intracranial pathology [1—3]. These disorders can exist preoperatively or develop during surgery or in the postoperative period. Preoperatively diagnosed hemostasis disorders are apparently the most favorable situation, since it is possible to prepare and inject the missing hemostatic factors before planned neurosurgical intervention, when necessary [4]. The situation is much worse when the pre-existing hemostasis disorder is subclinical and for the first time manifests in the form of hemorrhagic complications of surgical treatment. We have been recently faced with such a clinical situation in our practice.

Case report

Patient P, 51 years old, body weight 111 kg, height 186 cm. BMI 31 kg/m2, was admitted to our clinic for planned operation with the diagnosis of a giant meningioma of the wings of the sphenoid bone on the left. At admission, the patient complained of headache, nausea, vomiting, impaired vision and hearing. These complaints developed quite abruptly, one month before admission, and were accompanied by increase in blood pressure to 180/100 mm Hg. They were attributed to hypertensive crisis and stopped by hypotensive therapy. However, MRT of the brain in 2 days showed the real situation: it was found that the patient had a large tumor, most likely meningioma of the wings of the sphenoid bone on the left with hyperostosis and moderate peritumoral edema (Fig. 1).

At admission, patient’s condition was relatively satisfactory. The patient is hypersthenic with overweight. Hypertension with working blood pressure of 140—50/90 mm Hg and periodic rises to higher values was the only apparent concomitant somatic pathology. The patient received chronic perindopril (75 mg) and amlodipine (5 mg) treatment. Tests showed normal values, except for a moderate decrease in platelet count to 106 000/µL (the lower limit is 150,000) and slight increase in creatinine (121 µmol/l, while the lower limit is 115). The life history did not give rise to “hemorrhagic” alertness. The study of the hemostatic system state using the standard set of tests found no significant abnormalities except for insignificant prolongation of the APTT to
37.1 s (limits 25—35 s), prothrombin index 105% (limits 80—120%), INR 0.98, fibrinogen level 2.8 g/l (limits 1.7—4.4 g/l). The patient had no history of surgical treatment.

Given the presence of moderate thrombocytopenia in several consecutive blood tests, the patient underwent thromboelastography (TEG), which showed the borderline normocoagulation state: coagulation index (CI) value was 3.0 (the lower limit of the norm) and the latent time until the appearance of the first filaments of fibrin was 29.9 min (the upper limit is 27 min) (Fig. 2). Additionally, the patient was consulted by hematologists, who concluded that there were no contraindications to the neurosurgical operation. In case of possible massive blood loss, it was recommended to transfuse platelet concentrates and fresh frozen plasma (FFP). Furthermore, for the same reasons, the patient was included in the preoperative autodonation program, during which 900 ml of auto-FFP was prepared. Preoperative cerebral angiography was not carried out.

The patient underwent standard preoperative preparation and then he was taken to the operating room and operated on: resection of the meningioma of the wings of the sphenoid bone on the left. The operation was carried out under general anesthesia (i/v propofol infusion + i/v bolus fentanyl and rocuronium), mechanical ventilation with oxygen-air mixture in IPPV mode, normoventilation (ETC02 =37—41 mm Hg), and FiO2 =0.35.

Osteoplastic trepanation was carried out through the horseshoe-shaped incision in the left fronto-temporal region. DM was opened and a dense tumor node with extensive blood supply was observed. First, the basal fragment of the tumor was resected, which was accompanied by significant hemorrhage. Then, hyperostosis was resected using a drill, which was also accompanied by significant hemorrhage. Further, the anterior and then the medial part of the tumor was resected. Resection of the entire tumor was followed by coagulation of the site of the tumor with pneumocompression of the lower extremities and covering with a tacho-comb plate. Adequate surgical hemostasis was achieved. The total duration of the operation was 5.5 hours, blood loss was about 3 liters and it was compensated by infusion therapy (crystalloid solutions), auto-FFP transfusion + 340 mL of donated FFP + autoerythrocytes obtained after wound blood (1,600 mL) processing using Extra cell saver. The systemic hemodynamics values remained stable during the operation; hemoglobin and hematocrit values at the end of the operation were 12.9 g/dl and 38.6%, respectively; platelets — 95,000/μL. The tumor (histologically meningioma) was totally resected. At the end of hemostasis, there was no evidence of continued hemorrhage in the bed of resected tumor. At the end of the operation, the patient was transferred to the intensive care unit for dynamic follow up.

Clinical observation and control computed tomography (CT) data showed that the patient had hematomata in the bed of resected tumor with an intracerebral component in the left temporal lobe in the early postoperative period (1 hour after the end of the first operation) (Fig. 3). The patient was urgently taken to the operating room, where he underwent surgery, revision of the operating wound and removal of the hematomata. No bleeding sources were detected. The next morning after the operation and revision, the patient was in clear consciousness and followed instructions. Neurological status showed right-sided hemiparesis with decrease in muscle strength up to 3 points in the hand and up to 1—2 points in the leg, as well as elements of sensory aphasia.

Over the next 6 days, the patient’s condition improved: the level of wakefulness increased, the right-sided hemiparesis and speech disorders partially regressed. Mechanical ventilator was discontinued and the patient was extubated on day 6 after the operation. Neurological status: partially regressed hemiparesis on the right and elements of sensory aphasia. At this stage of treatment, the patient was once more consulted by a hematologist. Laboratory study of hemostatic parameters including TEG (Fig. 5) showed no serious deviations except for the borderline values of some TEG indices along with normal values of the coagulation index.

However, the situation changed since day 8 after the operation. There was slowly progressive worsening of patient’s condition in the form of decrease in spontaneous activity, increase in speech disorders, development of dysarthria and choking. Control CT showed no new intracranial hemorrhages. In connection with inadequate spontaneous breathing, the patient was intubated and received mechanical ventilation; the next day he was tracheostomized. A day later, bleeding from the tracheostome was observed, which gave occasion to the second consultation of the hematologist. Laboratory studies, including TEG, again showed no significant abnormalities. It was suggested that the fibrinolysis system could be activated, and therefore it was recommended to use fibrinolysis inhibitors (10 mg/kg of tranexamic acid) in combination with pneumocompression of the lower extremities for prevention of deep vein thrombosis.

Over the next 6 days, the patient’s condition was stable: the level of consciousness corresponded to deep stunning; there was deep right-sided hemiparesis without negative dynamics on CT.

Taking into account the hemorrhagic syndrome, the patient’s blood was sent for examination to the express laboratory of the intensive care unit of the Hematology Research Center (HRC) on the 13th day after the operation, where the study of chronometric values demon-
Fig. 1. Preoperative MRI of patient $P$.
Contrast-enhanced T1-weighted images.
Stratified prolongation of APTT to 50 s, while the rest of screening parameters were within the limits (fibrinogen 2.1 g/l, Quick prothrombin 63%, thrombin time 15 s). Normal thrombin time excluded the presence of heparin in blood samples. Since prolongation of APTT under these conditions could be caused by deficiency of the factors of the internal coagulation pathway, plasma activity of factors VIII (FVIII) and FIX was investigated, which was found to be 28% and 80%, respectively. Decrease in FVII activity to 28% did not fit into the diagnosis of hemophilia, and therefore patient's plasma was investigated for von Willebrand factor activity (FvW), whose decrease is often associated with moderate decrease in factor VIII). Ristocetin cofactor activity of FvW was 0%, FvW antigen — 29% Measurement of the amount of FvW antigen enables differentiating between quantitative deficit (where FvW:Ag decreases) and qualitative disorders (where its level does not decrease and FvW:RCO/FvW:Ag ratio is <0.7). The patient was diagnosed with von Willebrand disease (syndrome?). Hemostatic therapy with FVIII concentrate enriched with von Willebrand factor (Vilate) at a dose of 4000 was recommended and carried out. After injection of FVIII concentrate enriched with von Willebrand factor, APTT was 49 s, plasma activity of FVIII was 56%, ristocetin-cofactor activity of FvW — 2.9%, FvW antigen — 25%. The patient was repeatedly consulted by the hematologist, detailed laboratory study of the hemostasis system was performed at the specialized hemostasiology laboratory of the HSC, and type III von Willebrand disease was diagnosed (factor VIII — 27.6, von Willebrand factor — 0 (!), factor antigen — 20%). However, the patient's condition abruptly worsened next morning. There was arterial hypotension (BP 65/50 mm Hg), tachycardia (HR 120 per min), and
bilateral mydriasis. An emergency control CT scan revealed a large intracerebral hematoma in the left frontotemporal region (the size of the other hematomas was without dynamics), diffuse cerebral edema, pronounced dislocation of the median structures, the surrounding cistern was not found (Fig. 6). The patient was urgently taken to the operating room, where he underwent surgical wound revision with hematoma resection.

Despite the intervention, the patient was in grave condition: coma III, bilateral mydriasis, atony, areflexia. IVL, hemodynamics with a tendency to hypotension despite vasopressor support. The next day, the patient stopped cardiac activity with underlying extremely serious condition. Resuscitative measures were ineffective. Death was stated. The autopsy was not performed on the insistence of relatives.

Discussion

There is probably no other field of surgery (maybe except for ophthalmic surgery), where abnormalities in the hemostatic system can lead to such extremely severe consequences for the patient as in neurosurgery, especially in the case of intracranial interventions [2]. At the end of 2015, the respectable publishing house Thieme issued a book focusing on hemostasis disorders in neurosurgical patients, and this, in our opinion, is a serious indicator of the relevance of this problem [3]. Further more, the values obtained in several retrospective studies on postoperative hematomas in neurosurgical patients are very alarming. Thus, J. Palmer et al. [5], who analyzed more than 6,500 neurosurgical interventions, found that the incidence of postoperative hematomas was 1.1%, although in the case of meningiomas the incidence increased to 6.6%. Mortality associated with this complication was 32%! In 75% of complications, risk factors were retrospectively determined. I. Kalfas and J. Little [6] analyzed more than 4500 neurosurgical interventions and found the complication rate close to 0.8% (it was higher in patients with meningiomas). Most importantly, they identified two key factors in the development of this severe complication.

These two factors are: 1) hemostatic disorders in the form of hypocoagulation; 2) acute increase in blood pressure in the early postoperative period. Later studies have confirmed these findings [7, 8]. Thus, it is hemostatic disorders in the form of hypocoagulation that are the leading cause of postoperative hematoma after intracranial interventions. In connection with this, preoperative laboratory screening of the state of the hemostasis system in neurosurgical patients seems to be extremely important. But this is another topic for discussion and we will return to it later.

It is clear that hemostatic disorders can be congenital and acquired. Acquired hemostatic disorders are primarily drug induced. To date, numerous anticoagulants and disaggregants prescribed with and without indications currently have flooded our pharmaceutical market, and therapists, cardiologists, and cardiosurgeons prescribe these medications extremely extensively [2, 3, 9—11]. From the viewpoint under consideration, this is probably the most favorable situation, since we are at least warned about possible problems due to the fact of drug intake (unless, of course, the patient withheld this fact). To date, this problem has been solved for long-acting anticoagulants in the planned neurosurgery. A scheme of change to short-acting anticoagulants has been developed followed by their withdrawal just before the operation and renewed administration in a relatively safe period (2—3 days after the intracranial operation). The scheme was called “bridging” and proved its effectiveness and safety [3]. The situation with disaggregants is more complicated, but there are also some encouraging ideas in the form of bridging therapy by short-acting disaggregants [9, 10].

Let us return to congenital hemostatic disorders, and first of all to the von Willebrand disease, which took place in our case. This disease was described by Eric von Will-
Burdeno in 1926 in the inhabitants of the Aland Islands as an autosomal inherited hemorrhagic disease. Hemor-
rhages on mucous membranes and skin (ecchymosis, epistaxis, gastrointestinal hemorrhage, and menorrha-
gia) are the main manifestations of the disease [12, 13]. Subsequent studies have shown that the incidence of this pathology is quite high: 1—2% of the population (!) [13, 14]. Although we do not live on the Aland Islands, when considering this incidence of the disease in the population and the number of neurosurgical operations per year at the Burdenko Neurosurgical Institute (more than 7000), then, logically, we must face up to 70—140 of such patients per year. There is something to think about. The situation is further complicated by the fact that several types of von Willebrand’s disease have been currently described: type 1, type 2A, type 2B, type 2H, type 2M, type 3, thrombocytic pseudo-von Willebrand disease, and von Willebrand syndrome characterized by acquired deficiency of this hemostasis factor [1, 7]. Our patient was diagnosed with type III of the disease, the most dangerous in terms of hemorrhagic complications. Its insidiousness, as in our case, lies in the fact that it is often latent, and only sometimes manifests in the form of spontaneous hemorrhages in the central nervous system, gastrointestinal tract, and skin-mucous hemorrhages [1, 7]. This is a rare variant of pathology with the incidence of 1 case per 300,000—500,000 individu-
als [13]. However, the patients with type 3 disease and point mutations may have no clinical manifestations at all [1, 7], as it happened in our patient.

However, the situation theoretically, although unlikely, can be even more complicated. Indeed, our patient survived to 51 years, and he never was operated on, but he underwent extraction of teeth, and there were no signs of serious hemorrhagic complications. Therefore, we can assume that in this case we dealt with acquired paraneo-
plastic syndrome of von Willebrand rather than von Wil-
lebrand’s disease. Unlike von Willebrand disease, ac-
quired von Willebrand syndrome occurs during life and is associated with various diseases: lymphoproliferative (multiple myeloma, Hodgkin’s disease, etc.), myelopro-
liferative (polycythemia, essential thrombocytopenia, chronic myelogenous leukemia), autoimmune (systemic lupus erythematosus), and hereditary (Gaucher disease) diseases, as well as tumors; it can be induced by pharma-
ceuticals (valproic acid, levofloxacin, hydroxyethyl starches, etc.) [15, 16]. There are only scarce reports in the literature [15] on the development of the acquired von Willebrand syndrome in patients with tumors. Most often, these are nephroblastomas, carcinomas, and neuroectodermal tumors. The late development and mani-
festation of hemorrhagic syndrome in our case also does not exclude the development of this syndrome as a re-
response to a tumor. It could develop as a result of selection of high molecular weight von Willebrand factor multim-
ers by tumor cells or the aberrant expression of GPIb or GPIb/IIIa receptors by a tumor [17]. It should be noted that acquired hemorrhagic syndromes caused by produc-
tion of antibodies to blood clotting factors are not rare and occur in many tumors, including tumors of the cen-
tral nervous system. The acquired hemophilia with the development of antibodies to factor VIII in a patients with glioblastoma has been reported [18]. At the same time, it was reported that antibodies to coagulation fac-
tors, in particular, to factor VIII, can be produced in re-
response to surgical treatment itself [19, 20]. Perhaps the release of antigens into the blood, such as clotting factors, during neurosurgical intervention can contribute to pro-
duction of antibodies against these antigens. This can al-
so explain the absence of significant changes and hemor-
rhagic syndrome in the first operation.
The use of perindopril can be another possible cause of von Willebrand syndrome in our patient. Perindopril is an ACE inhibitor. A large European placebo-controlled study aimed at evaluating the efficacy of perindopril showed that its administration during the year significantly decreases the level of von Willebrand factor [21]. However, this decrease was not clinically significant and could not affect hemostasis.

The literature reports cases of manifestation of von Willebrand’s disease in patients who underwent ENT and neurosurgical interventions, and outcomes were not always favorable [22, 23]. Favorable outcomes occurred in the case of type 2 and, in particular, when the disease was diagnosed preoperatively and surgical treatment was carried out using factor concentrate.

Unfortunately, the data on screening for von Willebrand’s disease, are also not very comforting. It was suggested to rely primarily on clinical manifestations of pathological hemorrhage, which may or may not be present, or pathological hemorrhage associated with surgical intervention [1, 7, 24], which was the case in our patient. The screening laboratory parameters of the hemostasis system are not very informative in this case, as evidenced by our observation. Only the APTT index was slightly increased (to 37.1 s compared to the limits of 25—35 s). But how to understand this increase, if the test is not standardized, the reagents produced by various manufacturers differ in phospholipid composition and activator type, and, as a consequence, have different reference intervals? Furthermore, only exclusive laboratories specializing in fine studies of hemostatic system parameters can currently determine von Willebrand factor in the blood and its antibodies. Unfortunately, the situation seems to be unresolvable so far. In this respect, the work of our German colleagues, focusing specifically on preoperative diagnosis of hemostatic problems, and applied to all surgical patients, including neurosurgical ones, is quite illustrative [25—28]. Interestingly, these specialists who deeply understand hemostasis also express a simple and understandable idea that complete preoperative laboratory diagnosis of the state of the hemostasis system in surgical patients is virtually impossible because of the complexity of this diagnosis and numerous hemostatic factors that should be verified. They believe that this seemingly unsolvable problem can be, first of all, solved using carefully collected history. According to the authors of the work, different questionnaires can be used for this purpose. The further diagnostic algorithm assessing the state of hemostasis system, which includes more complicated and expensive tests [25—28], was proposed based on the results of this questionnaire. Theoretically, screening tests can be supplemented by corrective tests, where factor-deficient plasma is used, even in a conventional laboratory. The next step is blood test in a specialized hematologic laboratory, which can give an opinion whether there is deficit of the factor. Apparently, it would be a good idea to perform ristocetin-induced platelet aggregation in a specialized laboratory in order to increase the reliability of the diagnosis of von Willebrand disease followed by TEG, aggregometry, and tests assessing the activity of individual factors. However, the role of TEG in this second-line diagnosis is not yet quite obvious to us, for example, based on the dynamics of TEG values in our patient.

Conclusion

The presence of hemostatic disorders in neurosurgical patients, especially without clinical manifestations, is really a life threatening situation, as evidenced by our case study. Screening of the state of the hemostasis system using conventional clinical tests is sometimes less informative in this situation.

The following approach seems to be the most adequate and effective of all approaches currently proposed in the world.

1. Careful history taking in neurosurgical patients sent for planned surgery. Special questionnaires that draw patient’s attention to micro-manifestations of possible latent hemostatic disorders are the simplest method to do it.

2. In case of suspicion for the presence of hemostatic disorders at any stage of treatment, conventional and then extended laboratory tests are required.

This approach will probably increase the frequency of preoperative detection of hidden hemostatic disorders and enable the development of corrective tactics and thereby prevention of severe postoperative complications.

Authors declare no conflict of interest.
The article was written in an interesting format of a scientific research detailing the main stages of the diagnosis and treatment of the patient supplemented by informal analysis of the causes of complications in this clinical case. When discussing this case, the authors used a large number of scientific pa-

Commentary

The paper analyzed the clinical case of a patient with a giant meningioma of the wings of the sphenoid bone. Despite the fact that the patient was carefully examined during preparation for routine surgical treatment, hemorrhagic complications were observed in the postoperative period. The problem of preoperative preparation and perioperative management of patients with brain injury is still relevant despite the progress in modern medicine. Formation of recurrent intracranial hematomas after neurosurgical intervention can significantly worsen clinical and neurological outcomes of the disease. Rapid formation of an additional intracranial space-occupying mass often leads to the development of dislocation syndrome accompanied by depression of the wakefulness level and progressive focal symptoms, which necessitate reoperation. Repeated operations, despite the positive effect and regression of neurological symptoms, increase the risk of infectious complications. Worsening of patient’s condition results in life-threatening situations, necessitate prolonged respiratory support, and increases the duration of the patient’s stay in the intensive care unit and in the hospital.

It is worth of mentioning that clinicians noted indirect signs of hemostatic disorders as early as at the stage of preoperative preparation and applied an unusual approach in diagnostic search. However, even the use of additional research methods (for example, thromboelastography) and consultation of hematologists did not show blood coagulation disorders. Increased hemorrhage during routine surgery and recurrence of intracranial hematomata even after the second operation forced specialists to continue laboratory studies of hemostasis, which did not show any serious deviations from normal values. The patient’s condition remained severe, requiring respiratory support and intensive care. Given the development of the systemic hemorrhagic syndrome, the patient’s blood sample was sent for examination to the express laboratory of the Hematology Research Center, where step-by-step analysis of the results showed decrease in plasma activity of factor VIII of the coagulation system and type 3 von Willebrand disease was diagnosed. The use of specific replacement therapy resulted in adjustment of hematostatic parameters towards normalization. However, on the same day, the patient had repeated of intracranial hemorrhage. Despite the surgical treatment, the patient’s condition was extremely grave and unstable. The next day, the patient died.
pers dealing with the problem of interest. This literature review helps to suggest possible causes of the syndrome of hemostatic disorders in the examined patient. Despite the fact that the aforementioned syndrome is a rare variant of the pathology, the concentration of patients with brain tumors that may have similar hemostasis disorders can be significantly higher in a specialized center. Currently, recurrent intracranial hematomas are quite common. In most cases, careful examination of these patients with a detailed analysis of coagulation system components is impossible. As a result, repeated intracranial hemorrhages are caused by incorrect surgical techniques, improper perioperative management of patients, fluctuations in blood pressure, and many others. A.Yu. Lubnin et al. logically demonstrated that routine diagnosis of these syndromes is highly complicated. The authors ask themselves, how to prevent the development of hemorrhagic complications associated with rare forms of hemostasis disorders. A thorough preoperative history taking and extended laboratory tests were suggested to be used in the cases of suspected hemostatic disorders in order to detect hidden disorders of the blood coagulation system.

The study deals with an extremely relevant issue of preventing the development of hemorrhagic complications in neurosurgical patients. When describing the case of treatment of one patient, the researchers describe in detail the state of the problem of hemostatic disorders in patients with brain tumors. The authors use their extensive experience and knowledge and present information in a skillful manner to make the reader think and consider clinical situations that arise in routine practice from a new viewpoint. The article can be useful not only to anesthesiologists, resuscitators, and neurosurgeons, but also to all specialists involved in treatment of patients with brain injury.

A.A. Solodov (Moscow, Russia)
A Favorable Outcome of Surgical Treatment and Intensive Care in a Child who Was Admitted in Severe Condition with Underlying Aneurysmal Subarachnoid Hemorrhage (Case Report and Literature Review)


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Treatment of children in the acute stage of hemorrhage from cerebral aneurysms is based on clinical cases reported in the literature and descriptions of small series of observations. There are no studies that enable the development of evidence-based approaches to intensive care in treatment of children with aSAH.

We present a clinical case with a favorable outcome of complex treatment in a child admitted to the Burdenko Neurosurgical Institute at an extremely severe condition.

The efficacy of treatment was based on a timely urgent neurosurgical intervention and adequate intensive therapy in the form of extended neuromonitoring with continuous measurement of intracranial pressure, which enabled using the whole complex of measures for timely management of intracranial hypertension.

A favorable outcome (a GOS score IV) after this severe aneurysmal SAH indicates that there are no absolute contraindications for neurosurgical treatment of children with cerebral aneurysms.

Keywords: arterial aneurysm, aneurysm in children, intensive therapy of SAH, acute period of SAH.

H. Eppinge [1] was the first who reported the aneurysm of cerebral vessels in a child in 1871. This pathology occurs in children only in 2.6% of all cases of cerebral aneurysms [2]. Anatomic and topographic features of childhood aneurysms different from those in adults have been described, but the effect of these features on the severity of aneurysmal subarachnoid hemorrhage (aSAH) and clinical manifestations of the acute period has not been adequately studied [3—5].

In the acute period of intracranial aneurysm rupture, the state of children is typically rated as satisfactory: Hunt—Hess grade I—II in 60—70% of cases [6—9]. Severe aSAH, which corresponds to Hunt—Hess grade I—V, was described only in 30% of cases. At the same time, the death rate of children with Hunt—Hess grade V can reach 82% [10].

It was reported that children, as well as adults, develop intracranial hypertension (ICH) and vasospasm in the acute period of aSAH. In this case, ICH is believed to be one of the leading causes of death. The incidence of delayed ischemic brain injury with underlying vasospasm in children is lower than in adults [10].

Severe aSAH accompanied by the development of ICH and vasospasm necessitate aggressive surgical tactics and intensive care (IC). In this situation, the basic principles of IC in children in the acute period of aSAH are adopted from “adult” practice. Obviously, the principles of therapy, whose effectiveness was proven in adults, cannot be unconditionally used in children.

Approaches to the treatment of children with intracranial aneurysms are based on published case reports and small series of cases. There are no studies that can form the basis for evidence-based approaches to intensive care in treatment of children with aSAH.

Since there are no recommendations on the management of children with severe aSAH and favorable outcomes are extremely rare in these patients, we report a case of severe (Hunt—Hess V) aSAH from an aneurysm of the middle cerebral artery (MCA) in a 8-year-old girl.

Case study

Patient E., 8 years old, was admitted to the Intensive Care Unit of the Burdenko Neurosurgical Institute on 24.09.15 with the diagnosis of the left MCA bifurcation aneurysm. Recurrent subarachnoid parenchymal hemorrhage with formation of hematoma at the left Sylvain fissure. Fisher 4, Hunt—Hess grade V.

At admission on day 2 after aSAH, the girl was in a coma: 4 points on the Glasgow coma scale. Neurologic examination showed mydriasis (D=S) and the lack of photoreaction. There was response to pain in the form of decerebration. Computed tomography (CT) and CT angiography of the brain showed aneurysm of the left MCA, subarachnoid-parenchymal hemorrhage with formation of a hematoma sized about 30 cm$^3$ at the left Sylvain fissure, lateral dislocation of the median structures by 6.5 mm, and compression of the surrounding cistern (Fig. I). Urgent correction of ICH (sedation with propofol, hyperventilation, hyperventilation) resulted in positive dynamics of neurological symptoms in the form of pupil narrowing and photoreaction on both sides. Later on, mechanical ventilation (MV) parameters were selected so that to provide normoventilation: PaCO$_2$ within the range 35—45 mm Hg and PaO$_2$ within the range of

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Invasive monitoring of blood pressure (BP) was started, systemic BP without vasopressor support was 100/60—110/70 mm Hg, heart rate — 77—90 beats per minute.

In connection with clinical and radiologic picture of cerebral edema and dislocation of the median structures of the brain as shown by CT, comatose state of the patient and the presence of response to emergency therapeutic manipulations, we decided to perform an urgent neurosurgical operation. Neurosurgical intervention was carried out within one and a half hours after child's admission, including clipping of the left MCA bifurcation aneurysm, removal of the intracerebral hematoma of the left temporal lobe, external decompression of the skull on the left. The operation was completed by installation of Codman parenchymatous sensor into the left premotor area for intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring. The ICP was 2 mm Hg at the time of sensor installation. The next day after the operation, control CT of the brain showed that diffuse edema persisted (Fig. 2).

On day 2 after the operation, we attempted to stop sedation to assess the dynamics of neurological status. Sedation withdrawal led to increase in ICP from 12 to 25 mm Hg. In this regard, sedation therapy was renewed. Tracheostomy was carried due to prognosticated long-term MV. Transcranial Doppler sonography (TCDS) showed increase in the linear blood flow velocity (LB-FV): the peak LB-FV in the left MCA was 250 cm/s, right MCA — 170 cm/s. These data suggested the development of vasospasm in the left MCA.

On day 3, there was stable increase in ICP to 30 mm Hg despite the sedation and anesthesia. Hyperosmolar therapy, hyperventilation, and deepening of sedation led only to a short-term effect. Later on, hypernatremia developed with Na level of 155—165 mmol/l. TCDS showed increase in the blood flow velocity: peak LB-FV in the MCA was 300—310 cm/s on the left and 200—220 cm/s on the right. CT of the brain was performed in connection with negative dynamics of patient’s state (Fig. 3), which showed pronounced edema and formation of a large ischemic lesion in the left hemisphere. The ventricular system and basal cisterns were visible. Differential diagnosis of vasospasm and post-dislocation circulatory disorders was carried out using direct angiography which did not confirm pronounced angiospasm in the left carotid system (Fig. 4).

Given the increase in ICP (there were episodes up to 65 mm Hg) despite sedation and anesthesia, lack of reserves for the use of hyperosmolar solutions and hyperventilation, external hypothermia with a target body temperature of 32—34°C was used. Additionally, external ventricular drainage (EVD) was placed to control ICH in the anterior horn of the right lateral ventricle. Norepinephrine infusion was started at a dose of 0.05—0.1 µg/kg/min to maintain adequate CPP (above 40 mmHg).

On day 5—7 after the operation, the patient developed anisocoria D<S and of cough reflex suppression. ICP ranged 30—60 mm Hg, CPP was maintained at a target level above 40 mm Hg. Hypothermia was maintained at 33°C.

On day 8, there was increase in negative dynamics in the form of bilateral mydriasis, suppression of all segmental stem reflex, and diffuse decrease in muscle tone. There was persistent strong ICH (ICP of 30—65 mm Hg). The doses of norepinephrine varied up to 0.5 µg/kg/min, which maintained the target CPP values of more than 40 mm Hg.

On day 10 day of therapy, positive dynamics was observed in the form of normalization of the left pupil size and cough reflex recovery. Controlled hypothermia was stopped (warming to normothermia was carried out during 24 hours). ICP mostly remained within the normal range with rare increases to 40 mm Hg during the day. The CPP corresponded to the target values.

On day 13, there was positive dynamics in neurological status, including movements in the left extremities in response to a pain stimulus. ICP was within the range of
15—25 mm Hg with underlying sedation and hyperosmolar solutions. Vasopressor support was stopped.

On day 18 after aSAH and surgery, the patient began to slightly open her eyes, there were spontaneous flexion movements in the limbs and oromandibular activity. The condition was regarded as vegetative. ICP was normal, 11—17 mm Hg, with underlying open EVD. EVD closure resulted in ICP increase to 25—30 mm Hg.

Taking into account patient’s dependence on the EVD, ventriculo-peritoneal shunting (VPS) was carried out on the right. ICP monitoring was discontinued on day 20 after aSAH.

CT on day 22 after aSAH showed separation of the ventricular system and dilation of the left lateral ventricle. EVD was installed in the left lateral ventricle. Later on, ventriculostomy of the right and left ventricles was carried out followed by right VPS.

On day 28 after aSAH, the patient followed simple instructions and was capable of spontaneous breathing through a tracheostomy tube. CT showed pronounced post-ischemic disorders in the left cerebral hemisphere. There was no hydrocephalus with VPS (Fig. 5).

In 30 days, the girl was transferred from the intensive care unit to the neurosurgical department for further therapy. On day 68 day after the operation, patient’s condition corresponded to 3 points on the Glasgow outcome scale and she was transferred to rehabilitation center.

A few months later, fronto-parieto-temporal cranioplasty was carried out on the left at another neurosurgical hospital and VPS was removed in connection with its dysfunction.

Two years after aSAH, the girl has practically no restrictions in everyday motor activity, independently walks, talks, attends school in spite of pronounced cystic glious changes in the left hemisphere (Fig. 6). Right-sided hemiparesis up to 4 points is the only remaining focal neurological symptom. To date, patient’s condition corresponds to GOS IV.

Discussion

Severe aSAH (Hunt—Hess grade IV—V) is rare in children. Thus, severe aSAH corresponding to grade V was observed only in 35% of 1165 pediatric patients described in the review of A. Sorteberg et al. [10]. The death rate in this group was 82%, while relatively favorable outcomes as assessed by GOS (GOS III) were achieved only in 13% of cases (see Table). As can be seen from the Table, GOS III is the most favorable outcome of aSAH in children with initial Hunt—Hess grade V aSAH.

Our case study demonstrates the best treatment outcome compared to those in the literature. What contributed to this result?
The patient was admitted in coma with suppression of segmental stem reflexes at the midbrain level and pons with signs of dislocation of the median structures of the brain and complete replacement of spontaneous breathing with mechanical ventilation. However, osmotherapy and hyperventilation resulted in improvement of patient’s condition. Given the fact that the brain stem was not yet irreversibly damaged, we decided to carry out an emergency neurosurgical intervention. Clipping of an aneurysm, removal of an intracerebral hematoma, and decompressive hemicraniectomy was carried out. We will not describe in detail the characteristics of neurosurgical interventions in children with SAH, since this aspect of treatment was detailed by Sh.Sh. Eliava et al. [2]. However, it should be noted that favorable outcome would be impossible in this patient without timely and adequate neurosurgical tactics. Hemicraniectomy and EVD significantly improved severe ICH. Clipping of the aneurysm enabled further hyperdynamic therapy and maintaining the target CPP values despite the episodes of severe ICH. Furthermore, strict adherence to the protocols developed at the Burdenko Neurosurgical Institute for prophylaxis of hospital-acquired infections prevented the development of meningitis in the postoperative period.

Comprehensive neuromonitoring was an important aspect of effective IC. Real-time monitoring of ICP enabled timely adjustment of IC.

At present, there are no IC protocols for children with aSAH developed from the perspective of evidence-based medicine. Pronounced and stable ICH was the main factor of secondary brain injury in the aforementioned case. The principles of IC aimed at preventing and correcting ICH have been adopted from the practice of treatment of adult patients and protocols for treatment of children with severe traumatic brain injury, including decompressive trepanation, external ventricular drainage, sedation, osmotherapy, hypothermia, etc. However, the patient had progressive ICH despite all the measures taken. Based on the protocol for treatment of children with severe traumatic brain injury [11], it was decided to strictly maintain the CPP at the level of 40 mm Hg or higher to prevent brain ischemia with underlying severe ICH. This was possible only with continuous invasive monitoring of the average BP and ICP [13—17]. There were episodes of ICP increase to 65 mm Hg. In this situation, the required average BP within the range of 80—90 mm Hg was achieved by increase in the dose of continuously injected sympathomimetic (norepinephrine) and increase in the rate of intravenous infusion (colloidal and crystalloid solutions). This persistent and aggressive IC tactics aimed at maintaining optimal CPP led to stabilization and subsequent improvement of the girl’s condition on the 10—21st day after aSAH.

Vasospasm is one of the most significant causes of delayed cerebral ischemia and unfavorable outcomes in adult patients with aSAH. The situation is somewhat different in children. Angiographic vasospasm is quite common in children. Thus, J. Ostergaard and V. Voldby [6] showed that, according to angiography, vasospasm devel-

Fig. 4. Patient E., 8 years old. Left-sided carotid angiography (3 days after surgery). There are no signs of pronounced angiospasm.

Fig. 5. Patient E., 8 years old. CT of the brain (day 28 after surgery). Postischemic disorders in the left hemisphere of the brain and in the anterior cerebral artery system on the right. Condition after the VPS.
ops in 53% of children with aSAH, but clinical manifestations of vasospasm in the form of additional neurological deficit are extremely rare. These data suggest that vasospasm, which leads to the development of delayed cerebral ischemia in adults, is not so dangerous in children with aSAH. This tolerance can be possibly attributed to well-developed collateral blood flow [5]. One study showed that only 3 of 17 children with angiographic vasospasm had clinical manifestations and they had less developed collateral blood flow [18].

In the case described in this article, the development and dynamics of vasospasm was initially evaluated using TCDS. Starting from day 2 after aneurysm rupture, the growth of LBFV was observed. On day 3 after the neurosurgical treatment, repeated CT showed postischemic edema in the left hemisphere. The causes of the development of ischemia were verified using direct angiography, which showed that there was no pronounced vasospasm. Probably, formation of an ischemic lesion resulted from dislocation syndrome.

Should the growth of LBFV force the clinician to take measures for the purposeful treatment of angiospasm in children? In children, the use of vasospasm criteria adopted in adult patients with aSAH leads to significant overdiagnosis of vasospasm. According to P. Moftakhar et al. [18], only 1 out of 12 children diagnosed with angiospasm based on TCDS according to adult criteria had a spasm confirmed by angiography; none of these children had clinical manifestations.

**Conclusion**

In the reported case, the outcome of the disease was relatively favorable despite the extremely severe condition of the patient at admission to the Burdenko Neurosurgical Institute rated as Hunt—Hess grade V. Two years after aneurysm rupture, the patient can talk, walk with little support, and continues schooling.

The effectiveness of treatment was determined by timely urgent neurosurgical intervention, which facilitated ICH control, and adequate IT in the form of extended neurmonitoring with continuous measurement of ICP, which enabled using the whole complex of measures aimed at timely management of ICH.

Clinicians excluded severe vasospasm as a factor of secondary brain injury by complementing the diagnostic complex with direct angiography.

A favorable outcome (GOS IV) after such a severe aneurysmal SAH suggests that there are no absolute contraindications for neurosurgical treatment of children with cerebral aneurysms. Adequate IC is possible only under conditions of advanced neurmonitoring. All vital functions can be restored even under the condition of prolonged ICH and further rehabilitation can return the patient to a full life.

**Authors declare no conflict of interest.**

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**Fig. 6. Patient E., 8 years old. CT of the brain (2 years after aSAH).**

Cystic glious changes in the left hemisphere and in the anterior cerebral artery system on the right.

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**The incidence of functional outcomes (GOS) in children with intracranial aneurysms depending on the severity of the condition at admission (A. Sorteberg and D. Dahlberg [10])**

<table>
<thead>
<tr>
<th>Patient condition</th>
<th>Good outcomes</th>
<th>Poor outcomes</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GOS—V</td>
<td>GOS—IV</td>
<td>GOS—III</td>
</tr>
<tr>
<td>Unruptured aneurysms,%</td>
<td>66</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Hunt—Hess I,%</td>
<td>85</td>
<td>11</td>
<td>2</td>
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<tr>
<td>Hunt—Hess II,%</td>
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<td>12</td>
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<td>Hunt—Hess V,%</td>
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REFERENCES


Commentary

Aneurysms and aneurysmal hemorrhages are rare in children. There are only scarce publications on the topic. This article reports another case in the general bank of knowledge on this issue.

The authors demonstrated successful treatment of a 8-year-old child with severe aneurysmal SAH (Hunt—Hess grade V). The child’s condition was accompanied by pharmacoresistant intracranial hypertension. It is important to emphasize that the probability of a fatal outcome was extremely high.

This case showed that a combination of timely adequate surgical tactics and further intensive therapy under neuromonitoring conditions can provide a good outcome in children.


Zh. B. Semenova (Moscow, Russia)
**The Transpalpebral Keyhole Approach in Surgery of Orbital Cavernomas: a Case Report and Literature Review**

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**Aim** — currently, there are many different surgical approaches to orbital pathology. This pathology rarely occurs in neurosurgical practice, and neurosurgeons have often used approaches that can be accompanied by negative cosmetic and functional outcomes.

**Material and methods.** We present a case report of orbital cavernoma removal via a minimally invasive approach.

**Results.** The presented case demonstrates successful removal of orbital cavernoma using the transpalpebral approach: a skin incision along a natural fold of the upper eyelid and orbitofrontal keyhole craniotomy. In the postoperative period, existing symptoms regressed; the patient assessed the cosmetic effect as excellent.

**Conclusion.** The transpalpebral keyhole approach can be an excellent alternative to traditional approaches to orbital cavernomas. This approach demonstrated its efficacy and safety in skull base surgery and provided excellent functional and cosmetic outcomes.

**Keywords:** orbital cavernoma, keyhole neurosurgery, cosmetic and functional outcomes, transpalpebral approach.

Orbital cavernomas (cavernous angiomas, cavernous hemangiomas) are rare primary intraorbital lesions. In classifications, orbital neoplasms are usually referred to benign vascular mass lesions because their structure and clinical manifestations are different from those of central nervous system cavernomas that are vascular malformations [1—3].

The treatment tactics range from observation to surgical removal indicated to patients with clinical symptoms, such as reduced vision, oculomotor disorders, progressive painful exophthalmos, and symptoms of a gradual increase in intraocular pressure [4—7].

The choice of a surgical approach is based on the neoplasm size and location. Traditionally, three main approaches are used: 1) lateral orbitotomy; 2) transconjunctival approach; 3) frontotemporal craniotomy (pterional or supraorbital approach) [3].

We report a clinical case of orbital cavernoma removal using the transpalpebral keyhole approach with a skin incision along a natural fold of the upper eyelid.

**Clinical case**

A 53-year-old female patient I. presented to the neurosurgical department with complaints of intermittent headaches, pressing pains and reduced vision in the right eye, diplopia, and right ptosis.

According to a medical history, the first symptom was headache that developed in 2015; the patient had no outpatient examination. Two months before hospitalization, the patient noticed a decrease in right eye vision and diplopia. Later, pressing pains developed.

Examination by an ophthalmologist revealed a decrease in visual acuity to 0.6 on the right. There was axial exophthalmos on the right with a difference of up to 4 mm (Fig. 1). Visual fields were normal. Upward movement of the right eyeball was restricted; diplopia mainly on upward and lateral gaze. There was ptosis on the right. The findings of the fundus examination were as follows: the optic nerve disc was of pale pink color, with blurred boundaries; the veins were dilated, plethoric.

MRI of the brain revealed a space-occupying lesion of the right orbit in the intraconal space with an elevated MR signal in T2, STIR, and DWI modes, which was located above the eyeball in the periorbital fat tissue, about 20×14×16 mm in size, round in shape, and with clear contours. The lesion was adjacent to the superior orbital wall and deformed it. There were signs of orbital roof destruction with preservation of a thin bone plate on the dura mater (Fig. 2).

Given the patient’s complaints, clinical symptoms, and MRI data, a decision was made to resect the neoplasm using the transpalpebral approach and orbitofrontal keyhole craniotomy. The patient was informed about alternative extended approaches to this pathology.

Planning of a skin incision and assessment of a natural fold of the upper eyelid were performed before transfer of the patient to the operating room. In addition, the anatomy of bone structures, size and volume of the frontal sinus, and location of the supraorbital notch were critically evaluated (Fig. 3).

Intraoperative preparation of the patient included the following stages. The patient head was fixed in the Mayfield frame and turned 30° to the left. An ophthalmologic antiseptic gel was placed behind the lower eyelid. Temporary tarsorrhaphy and treatment of the operating field with an aqueous antiseptic solution were performed.

The skin incision was performed along the natural fold of the upper eyelid from the level of the lateral border of the orbicularis oculi muscle to the lateral canthus. The incision extended up to the supraorbital notch. Given the patient’s complaints, clinical symptoms, and MRI data, a decision was made to resect the neoplasm using the transpalpebral approach and orbitofrontal keyhole craniotomy. The patient was informed about alternative extended approaches to this pathology.

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of the supraorbital notch. Subsequently, soft tissue dissection, careful manipulations with the orbicularis oculi muscle, and access to the supraorbital margin of the frontal bone were performed. After subperiosteal dissection of the supraorbital margin of the frontal bone, superolateral margin of the orbit, and zygomatic process of the frontal bone, a burr hole was made in the key point region using a high-speed burr, and an orbitofrontal key-hole craniotomy of about 2.5 × 2.5 cm in size was performed on the right. The frontal sinus was not opened. The projection and size of the frontal sinus were verified based on neuronavigation data. Orbital roof destruction in the form of significant thinning, up to cigarette paper thickness, was observed. The anterior part of the orbital roof was partially resected. The cavernoma was accessed in a sharp and blunt way using a microsurgical technique. The lesion, which was of a round shape, dark cherry color, and dense consistency, was separated from the surrounding tissues in a sharp and blunt way after coagulation and excision of the feeding arteries. An important stage of surgery was careful manipulation with the perifocal zone to minimize the risk of injury to the extracranial muscles and nerves. The neoplasm was totally resected (Fig. 4).

The wound was closed in layers; the bone flap was placed back and fixed with titanium plates; the skin was sutured using a continuous intradermal suture. Drainage was not used. There were no complications.

In the postoperative period, there was edema of the periorbital region, which regressed within 5 days. Exophthalmos, ptosis, and diplopia regressed; the patient was activated on the 1st postoperative day.

Figure 5 presents control CT scans of the brain with 3D reconstruction and control MRI scans of the brain 5 days after surgery.

In the early postoperative period, there was slight numbness in the supraorbital area; all symptoms completely regressed one month after surgery; the patient had no complaints. A patient’s image is shown in Figure 6.

Discussion

Orbital cavernoma is a fairly frequent primary neoplasm of the orbit in adults [8].

This tumor is more common in females; the peak of occurrence is the fifth decade of life [1, 10—12]. Di Tommaso found that expression of progesterone receptors in epithelial cells of orbital cavernomas may explain a high rate of their occurrence in females [6, 13].

The primary location of cavernomas is the middle third of the orbit, in the intraconal space. Conducted studies have found that the neoplasm is most often located outwards to the optic nerve [14, 15]. Involvement of the intraconal space in the pathological process leads to slowly progressing axial, sometimes painful exophthalmos, which is the most frequent first symptom of cavernoma (about 70% of cases). The degree of exophthalmos progression is different and amounts to about 2 mm per year, on average [16].

The second most frequent symptom is a decrease in vision. A series of studies have found that it occurs in 50%
of patients [7, 16]. Oculomotor disorders are present in 20 to 30% of patients [16]. Fundal changes can vary from optic disc pallor to optic disc atrophy, which may be caused by the cavernoma mass effect [16].

Paroxysmal symptoms are rare because orbital cavernomas, in contrast to intracranial cavernomas, have no tendency to hemorrhages [1, 10, 11]. As noted above, management of orbital cavernomas ranges from case follow-up to surgical removal. Symptomatic cavernomas are traditionally subject to microscopic total removal without serious complications in the postoperative period [4, 5, 7]. Studies have shown that the follow-up period in patients before the emergence of clinical symptoms ranges from 3 to 10 years [6].

Surgery of orbital cavernomas places a high value on careful preoperative assessment: the size and location of the neoplasm and its relationship with the orbit structures. Clear planning of the intended approach using all modern neuroimaging techniques is essential.

According to J. Maroon et al. [17] who in detail described approaches to the orbit, there are three main approaches to orbital lesions: 1) anterior medial mini-orbitotomy is used when the neoplasm is located in the anterior orbit; 2) the transcranial approach is the choice for all masses with intracranial growth or for those located in the orbital apex and extending to the optic canal; 3) lateral approaches are used if cavernoma is located in the superior, lateral, and inferior orbit.

Anterior orbitotomy is often used for both intracranial and extracranial lesions, excluding lesions in the orbital apex, which accounts for almost 60% of cases [18—20]. When the transconjunctival approach is used, opening of

Fig. 3. Planning of the transpalpebral approach.
a, b — planning of a skin incision; c — preoperative planning of an intended amount of craniotomy.
the conjunctiva and fixation the extraocular muscles are followed by placement of silk sutures near the site of muscle attachment for retracting the eyeball from the cavernoma [19, 21]. Sometimes, the extraocular muscles need to be separated near the site of their attachment to ensure adequate visualization [4]. Suturing of the neoplasm and its gentle traction during dissection are also permissible [4, 22—24]. Complications of this approach include eyelid hematoma, mydriasis, and loss of vision due to direct injury to the optic nerve or occlusion of the ophthalmic artery. H. Kiratli et al. [25] reported 24 patients who were operated on for intraconal cavernomas using the transconjunctival approach. In 8 (33.3%) patients, vision improved; in the other patients, there was no improvement. None of the patients had any worsening.

In a multicenter study by B. Bleier et al. [26], the endoscopic transnasal approach to the orbit was used. Out of 23 patients, 17 (73.9%) patients underwent total removal of cavernomas; in 78.3% of patients, there was regression of eyeball asymmetry. Also, comparison of postoperative complications associated with the location of cavernomas (intraconal or extraconal) was performed. Lateral orbitotomy and the transcranial approach are more traumatic than the transconjunctival approach, and they are used mainly for tumors located superior or lateral to the optic nerve and eyeball [27]. In 1889, R. Krönlein [28] first described lateral orbitotomy that became the most preferred approach to orbital lesions. A. McNab and J. Wright [15] presented their experience of treating 85 patients with cavernous angioma of the orbit; of these, 71 patients were operated on using lateral orbitotomy, with 3 (4.23%) patients developing loss of vision in the postoperative period. Transcranial approaches can be used when cavernoma is located in the posterior third of the orbit. Neoplasms can be resected both extradurally and intradurally. According to the authors, potential complications included convulsive seizures, subdural hematomas, and transient loss of vision [3, 6, 29]. P. Misiori and co-authors [30] were the first who used the transcranial approach for resection of cavernous angiomas of the orbit in 23 patients. Three (13%) patients developed ptosis; 8 (34.9%) patients had decreased vision after surgery. In another series of patients presented by N. Acciarri et al. [1], only 1 (7.7%) of 13 patients had a decrease in vision after frontal craniotomy. M. Maus and H. Goldman [31] used transorbital craniotomy with an eyebrow skin incision to remove cavernoma of the orbital apex; there were no complications in the postoperative period. However, the eyebrow skin incision compared to the

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Fig. 4. Stages of orbital cavernoma removal. Intraoperative images.

a — view after transpalpebral craniotomy, 1 — orbital septum covering the eye and orbital structures, 2 — dura mater over the frontal lobe pole on the right; arrows indicate a partially resected roof of the orbit; b, c — stage-by-stage dissection of the cavernoma, C — cavernoma, PF — peri-orbital fat; d — appearance of the resected cavernoma.
Fig. 5. Postoperative neuroimaging data.
a, b — CT scans with 3D reconstruction; c—e — control MRI scans of the brain.
transpalpebral approach carries a certain risk of injury to the facial and trigeminal nerve branches, which may be accompanied by negative cosmetic and functional outcomes.

Vertical transpalpebral anterior orbitotomy is also one of the approaches to the medial intraconal space. This approach was first proposed by B. Smith in 1966 [32]. R. Kersten and D. Kulwin [33] presented a series of patients operated on using this approach. In 7 (77.8%) patients, there was blepharoptosis after surgery. In the domestic literature, Ya.O. Grusha and co-authors [34] reported a case of orbital cavernoma resection using vertical transpalpebral orbitotomy. In the postoperative period, all symptoms gradually regressed; there were no complications.

In the present study, we used the approach to the cavernous orbit, which had not yet been applied in neurosurgical practice. The transpalpebral keyhole approach with an incision through the natural fold of the upper eyelid and orbitofrontal craniotomy may be an excellent alternative to all of the approaches discussed above. This approach eliminates complications associated with traditional extended approaches. The goal of surgical intervention is to preserve visual functions. Using the concept of keyhole surgery, we have achieved favorable functional and cosmetic outcomes, which indicates the effectiveness and safety of this approach to orbital lesions [35, 36].

Conclusion

The transpalpebral approach can be successfully used for orbital neoplasms to achieve excellent functional and cosmetic outcomes.

The choice of a surgical approach is determined by the size and location of cavernoma and is based on careful preoperative planning. There are single reports on the use of transpalpebral craniotomy in surgery of orbital cavernomas; therefore, further evaluation and critical selection of patients are needed.

Authors declare no conflict of interest.

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Fig. 6. Image of the patient one month after surgery.
maining thin (as cigarette paper) bone layer on the dura mater about 1/3 of the orbit roof. According to our experience, a re
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duced the use of the transpalapebral keyhole approach in this patient. All of them were accepted.

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Commentary

The article by R.S. Dzhindzhikhadze and co-authors is devoted to the actual topic of surgical approaches to the skull base. At present, there is a tendency to use conservative, minimally invasive, and cosmetically effective approaches. The authors demonstrated the use of the transpalapebral keyhole approach for cavernous hemangioma of the anterosuperior orbit. One of the most complex issues is defining the indications for neurosurgical intervention with formation of a supraorbital flap and exposure of the dura mater. Tumors of this localization are usually removed by ophthalmic surgeons using the transconjunctival approach to the anterosuperior orbit. But in the case of orbital roof destruction with the risk of penetrating to the anterior cranial fossa base, ophthalmic surgeons refer these patients to neurosurgeons. In the present case, there was extensive bone destruction of the anterior cranial fossa base, which occupied about 1/3 of the orbit roof. According to our experience, a remaining thin (as cigarette paper) bone layer on the dura mater does not interfere with intracranial and even intradural penetration in the case of a narrow field of vision of the transconjunctival approach. In this case, repair of a dura mater defect is difficult, or even impossible. In this regard, I consider the use of this approach in the presented case reasonable. It should be noted that a Bulgarian neurosurgeon L. Karagezov was one of the first who described an analogous approach more than 50 years ago. He called the approach a “pullout drawer” technique, in which a flap of the supraorbital margin of the frontal bone was pulled out to remove orbital tumors, followed by placing the flap back (L. Karagezov, A new transcranial approach to the orbit. Voprosy Neirokhirurhii. 1967. No. 1. P. 5–8). In the initial manuscript, I had minor comments on the anatomical terminology and the reasonability of this approach in this patient. All of them were accepted.

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Traumatic brain injury and its consequences remain one of the leading causes of disability and mortality in working age individuals [1]. The development and implementation of the principles of evidence-based medicine into clinical practice improved the outcomes of treatment of patients in the acute period of severe traumatic brain injury [2—4]. However, decrease in mortality led to increase in the number of patients with consequences of TBI, including those with PTH. Hydrocephalus hampers recovery and rehabilitation of patients [5]. The relationship between the development of hydrocephalus and previous TBI has been established long ago [6, 7]. Its clinical and neuroimaging aspects have been investigated [8—10]. Nevertheless, it is difficult to recognize PTH in vegetative and minimally conscious state, and the number of unreasonable surgical interventions and, as a result, unsatisfactory outcomes of treatment is still high.

Severe condition of patients with PTH, the presence of concomitant pathology, and often low level of consciousness make them extremely vulnerable to infectious complications and decompensation of underlying chronic pathology. Even minimally invasive studies (lumbar puncture, external lumbar drainage, infusion tests) can cause exacerbation of chronic infections, decompensation of water-electrolyte, hormonal, and other disorders [10].

Currently, neurosurgeons mainly focus on the study of idiopathic normotensive hydrocephalus, while much less attention in paid to the problem of secondary hydrocephalus. This review includes the results of the search in the current international literature in the Medline system using the search query “posttraumatic (OR) post-traumatic hydrocephalus, secondary hydrocephalus, hydrocephalus (AND) traumatic brain injury”. The search covered the literature published since 1965, when S. Hakim [7] first described the so-called normotensive hydrocephalus in patients with consequences of TBI. A total of 65 literature sources were used.

**Pathomorphological background of the development of posttraumatic hydrocephalus**

Literature data on the incidence of PTH vary in a wide range from 0.8 to 95% [9, 11, 12], which, apparently, is associated with the erroneous inclusion of all patients with posttraumatic ventriculomegaly, including atrophy triggered by brain injury, into this category. The incidence of TBI-related PTH probably reaches 20% [9, 12]. Obstruction of CSF flow pathways in the subarachnoid

**Keywords:** traumatic brain injury consequences, posttraumatic hydrocephalus, secondary hydrocephalus, ventriculomegaly, consciousness recovery, shunting surgery, shunt infection.
spaces, which hinders adequate CSF resorption, is the main cause of pathological accumulation of CSF in the CSF system (similar to that in non-traumatic subarachnoid hemorrhages) [13—16]. Purulent-inflammatory complications in the acute period of TBI with underlying adhesive process is often followed by intraventricular obstruction of CSF pathways (at the level of the foramen of Monro, ventricular aqueduct, and openings of the fourth ventricle), as well as basal cisterns.

The development of hydrocephalus is mainly associated with initially more severe TBI [12, 17]. Widespread implementation of the methods for surgical correction of refractory intracranial hypertension in neurotraumatology practice reduced mortality in patients with severe TBI with focal and diffuse brain injury, but did not significantly improve long-term outcomes in survivors [4]. Some authors [18—20] noted possible relationship between the development of PTH and decompressive craniectomy in the acute period of TBI.

It is assumed that the development of hydrocephalus is affected by the size of decompressive trepanation, and especially location of its upper edge close to the midline (less than 25 mm) and, therefore, to the superior sagittal sinus [20]. Wide decompressive trepanation is a possible additional traumatic factor that worsens the state of the subarachnoid CSF flow channels [17]. Another hypothesis considers changes in volumetric ratios and gradients of CSF and venous pressure under conditions of opened skull as a cause of CSF resorption disorders [21]. It is believed that the pulsational CSF pressure in the subarachnoid spaces required for the functioning of the valvar resorption mechanism decreases, leading to decrease in CSF resorption [22].

The study focusing on the relationship between early cranioplasty and regression of CSF disorders [22] showed that closure of the skull defect within 35 days from the moment of decompression contributed to spontaneous regression of ventriculomegaly. The effect of decompressive craniectomy on the development of CSF circulation disorders should be further studied and clarified.

The main clinical manifestations of PTH

Clinical manifestations of hydrocephalus are variable and often present with a mosaic combination of symptoms of primary brain injury and secondary PTH. Hydrocephalus can be hypertensive or normotensive. There are no reliable data in the literature on the incidence of various types of PTH. It is not difficult to diagnose secondary hypertensive hydrocephalus, especially in patients with soft tissues prolapse in the trepanation hole. In these cases, the disease is represented by local manifestations in combination with general cerebral symptoms, local pain syndrome, or psychopathological symptoms [10, 12]. In the cases of normotensive posttraumatic hydrocephalus and in patients with low level of consciousness, it is often difficult to diagnose and determine indications for surgical treatment [23]. The course and clinical manifestations of normotensive PTH are largely determined by the degree of recovery of TBI patients. The symptoms of the classical Hakim triad develop along with decrease in the primary symptoms [7]. In these cases, examination is carried out according to international guidelines for the diagnosis and treatment of normotensive hydrocephalus with a set of tests including the tap test (dynamic neuropsychological testing and assessment of gait changes after lumbar puncture with CSF withdrawal) [24, 25].

The patients with severe TBI after a prolonged coma may demonstrate slower rate of consciousness recovery, which may be caused by normotensive PTH. A series of scales were proposed to assess the dynamics of psychopathological processes in these cases: the stages of consciousness recovery after a long-term coma, GOS-E, JFK Coma Recovery Scale-Revised, Nippon scale, etc. [26, 27].

If a TBI patient has ventriculomegaly and impaired consciousness, differential diagnostics between the atrophic process and normotensive PTH is required. In patients with posttraumatic hydrocephalus in the vegetative and minimally conscious state, the dynamic neuropsychological testing before and after the tap-test is impossible, and the dynamics of the level of consciousness is evaluated [5, 10, 28]. However, changes in the mental status after the tap-test are not always observed in these patients and may be biased by doctors and patient’s relatives.

Neuroimaging diagnosis of posttraumatic hydrocephalus

Neuroimaging methods are required to diagnose PTH. Routine CT and MRI in the standard modes are available and simple methods to detect ventriculomegaly. A number of pathognomonic features of PTH have been described: 1) balloon-like dilation of the anterior horns of the lateral ventricles; 2) dilation of the temporal horns and the third ventricle; 3) dilation of basal cisterns and the fourth ventricle; 4) periventricular areas of hypodense signal [8, 28]. Various indices are used to assess the degree of ventricular dilation and the dynamics of their size after treatment: Evans index, the ratio of the size of the frontal and occipital horns of the lateral ventricles (FOHR — frontal-occipital horn ration), and a number of MR-volumetric techniques [29—32].

Of course, even the characteristic neuroradiological criteria of hydrocephalus cannot be used as indications for surgical treatment [33]. New modalities of MRI are used for non-invasive diagnosis of hydrocephalus. A number of techniques (MR-cisternography) can detect intraventricular occlusion and assess the state of basal cisterns and convexital subarachnoid spaces [29]. It was noted that disproportionately enlarged subarachnoid spaces (DESH) on coronary sections are more common in patients with normotensive hydrocephalus. MRI picture of DESH is characterized by compression of sub-
arachnoid spaces of convexal surfaces with underlying pronounced dilation of the lateral fissures (Fig.). A multicenter prospective cohort study in 100 patients considered DESH as an indication for surgery and positive effect of surgical treatment was observed in 89.0% of cases [34].

Phase contrast MRI with cardiac synchronization for evaluation of CSF circulation parameters in patients with ventriculomegaly is another modern method widely used to diagnose normotensive hydrocephalus. Various velocity and volume parameters of CSF circulation at the level of the Sylvian aqueduct of the brain were studied in patients with suspected normotensive hydrocephalus, healthy volunteers, and patients having ventriculomegaly with underlying cerebrovascular disease [35].

Mean flow (average volume of CSF passing through the Sylvian aqueduct per minute) and stroke volume (stroke CSF volume in the aqueduct during one cardiac cycle) demonstrated the greatest sensitivity and specificity with respect to hydrocephalus [36]. This type of CSF circulation was called hyperpulsatile, and some authors believe that it is pathognomonic for normotensive hydrocephalus and can be used as a sufficient prognostic criterion of shunt effectiveness. At the same time, other studies [37—39] showed low sensitivity of these CSF circulation parameters and demonstrated that they cannot be considered as the only predictors of the positive effect of the operation. It was also found that CSF circulation parameters can change and not correlate with clinical manifestations in the case of long-term hydrocephalus [40]. During the first year after the development of symptoms characteristic of hydrocephalus and corresponding MRI picture, CSF circulation parameters in the phase-contrast MRI were hyperpulsatile, but later normalized, although the clinical manifestations, on the contrary, progressed.

Modern modalities of MRI enable visualization of the anatomical and functional relationships between various brain structures and accurate detection of focal lesions. Detection of certain lesions, especially deep-seated ones, in the acute period of TBI may be predictive of unfavorable outcome [41]. Possibly, detection of some other focal changes in deep structures during preoperative examination of patients with PTH (especially those in vegetative and minimally conscious state) can also be considered as a predictor of unsatisfactory outcome of the bypass operation.

Ventriculomegaly is evidently associated with tension and compression of white matter fibers. In some studies, fractional anisotropy was measured by diffusion-tensor MRI in patients with idiopathic normotensive hydrocephalus. A number of studies have shown that the coefficient of fractional anisotropy decreases in the corpus callosum and increases at the posterior limb of the internal capsule, which correlates with the severity of clinical manifestations [42—44].

![DESH in a patient with posttraumatic hydrocephalus. Ventricles and lateral fissures are significantly enlarged in combination with compression of the sulci of the convexal surface of the brain.](Image)

In summary, along with routine methods of examination, the repertoire of neuro-radiological studies includes novel techniques, which may facilitate the diagnosis and treatment of PTH, but they have not been widely used in clinical practice so far.

**Treatment of PTH**

Normalization of volumetric intracranial ratios [10] is the main objective in treatment of hydrocephalus. Indications for surgical treatment are determined by clinical and X-ray data, indicating progressive accumulation of CSF. Currently, ventriculoperitoneostomy is the “gold standard” in the treatment of all types of hyporesorptive/aresorptive hydrocephalus [24].

Improvement of modern shunting systems enables differentiated approach to the choice of a shunting valve in each clinical case [28]. The development of programmable valves capable of non-invasive opening pressure adjustment enables selecting the optimal degree of CSF drainage for each patient and avoiding reoperations in the case of inadequate CSF drainage syndromes [45, 46]. Implantation of complex shunting systems with programmable valve opening pressure can be recommended in patients with normotensive hydrocephalus [47, 48].

Taking into account different variants of PTH, treatment can be differentiated. In the cases of confirmed occlusion, endoscopic tri-ventriculo-cysternostomy may be an alternative to ventriculo-peritoneostomy. However, taking into account the hyporesorption/aresorption states accompanying PTH, this technique may be ineffective [10, 28, 49].

In summary, modern repertoire of treatments for PTH and a wide variety of shunting systems enables indi-
vidual selection of the type and tactics of the operation, and, in some cases, avoiding implantation of a foreign body into the ventricular system. Nevertheless, there are no analytical studies on the effectiveness of endoscopic interventions for PTH in the literature [49].

Purulent-inflammatory complications of bypass surgery

Purulent-inflammatory complications are the most dangerous complications of surgical treatment for hydrocephalus. The incidence of shunt infection varies between different clinics and different surgeons and averages 1—15% [50—52].

Prophylactic administration of antibiotics is advisable when planning bypass surgery [50, 51, 53]. Refraining from shaving hair with a razor, using two pairs of gloves to remove the second pair before catheter implantation, using suture material impregnated with antibiotics, and apodactyl (without touching the wound) manipulations significantly reduce the risk of infection [54].

Currently, catheters for shunting systems impregnated with antibacterial drugs (rifamycin and clindamycin) are being used. The data from the British bypass surgery registry shows that the incidence of infection is 5% lower when using catheters [55]. Other authors [56] demonstrated the absence of significant decrease in the incidence of shunt infection in this situation in patients who were operated at the same clinic. A large American retrospective study of risk factors for shunt infection analyzed 12,589 bypass operations in 600 clinics. It has been shown that the use of antibiotic-impregnated catheters reliably reduces the incidence of shunt infection by 1.4% in adults and 4.5% in children [57].

In cases of confirmed shunt infection, treatment tactics is based on the earliest possible complete removal of the shunting system in combination with administration of broad-spectrum antibiotics until the results of inoculation test are obtained [51, 52]. If the patient is shunt dependent, external drainage of CSF from the ventricles or withdrawal through the lumbar catheter in carried out during CSF sanitation [10, 58]. Repeated bypass surgery is performed when the liquor is completely sanitized and the culture is sterile [59].

Shunting system dysfunction. Inadequate CSF drainage syndromes

According to the large study of the effectiveness of bypass surgery for various types of hydrocephalus in the United States, it has been shown that about 80% of all shunting systems fail for one or another reason 10—12 years after implantation [60]. Dysfunctions of shunting systems clinically manifest in the form of inadequate CSF drainage syndromes.

CSF hyperdrainage is one of the most common complications of bypass surgery and its incidence reaches 20—30% [10, 61, 62]. Hyperdrainage syndrome can be associated with incorrect choice of the shunt valve opening pressure and/or the siphon effect of patient’s verticalization [10, 28, 63, 64]. The clinical picture of CSF hyperdrainage is variable, but usually manifests in the form of increase in focal and general cerebral symptoms. Hyperdrainage may be accompanied by isolation of cerebral ventricles, slit-ventricle syndrome, subdural hematomas and hygromas often develop [10, 62].

Inadequate drainage syndromes are caused by mechanical factors, such as ventricular catheter obstruction (for example, with vascular plexus), disconnection or migration of catheter ends (both ventricular and peritoneal), disconnection of shunting components, development of abdominal pseudocysts, or inadequate drainage by the shunting valve [10, 62]. Manifestations of insufficient CSF drainage include negative dynamics of patient’s neurological status, which returns to a preoperative level.

As noted above, the use of modern programmable valves enables pressure adjustment without replacement and reoperations, and, in some cases, elimination of accumulated subdural CSF and even chronic subdural hematomas without additional surgical intervention [46—48, 64]. Antisiphon (gravity) devices can be used to reduce the incidence of complications associated with hyperdrainage during patient’s verticalization [65].

Conclusion

Posttraumatic hydrocephalus remains a serious underestimated consequence of TBI that hampers patient’s recovery. The use of modern diagnostic methods enables differentiated approach to the treatment of PTH in a particular patient, and the use of programmable shunting systems personalizes treatment and, in some cases, prevents reoperations. Nevertheless, there are still unresolved issues of diagnosis and prevention of treatment complications in patients with PTH. There are no objective data on changes resulting from CSF circulation disorders, their reversibility, and correlation with clinical presentation. All the above in combination with high risk of purulent-inflammatory complications, serious condition of patients, and the lack of reliable prognostic criteria of operation effectiveness, especially in patients in the vegetative and minimally conscious state, determine the direction of further research and the need to systematize the available clinical experience in the treatment of PTH.

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Traumatic brain injury and its consequences are urgent problems of neurosurgery. The article discusses modern aspects of the diagnosis and treatment of posttraumatic hydrocephalus, which is one of the common consequences of severe traumatic brain injury.

The authors discuss the main clinical manifestations of posttraumatic hydrocephalus, diagnostic methods, including the advanced modalities of magnetic resonance imaging, which provide data on individual anatomical and CSF circulation features in patients with this pathology. The authors discuss the weaknesses and strengths of the modern MR-criteria suggested for non-invasive diagnosis of posttraumatic hydrocephalus.

Although the treatment for hydrocephalus has been developed a long time ago, the problem of purulent-inflammatory complications of CSF-shunting operations and complications associated with bypass dysfunction remains unsolved.

The review presents current approaches to reducing the incidence of shunt infection developed in large studies based on the principles of evidence-based medicine.

Syndromes of inadequate CSF drainage and bypass dysfunction are discussed separately. The authors demonstrate the effectiveness of the use of programmable valves and anti-gravity devices to overcome these complications of CSF shunting surgery based on the modern literature and research.

Literature data analysis showed that posttraumatic hydrocephalus remains an underestimated consequence of TBI, affecting the recovery and rehabilitation of patients. Differential diagnosis should be further developed and improved. The use of validated effective methods for prevention of shunt infection and modern shunting valves in clinical practice improves the results of hydrocephalus treatment.

V.A. Lazarev (Moscow, Russia)
The 2016 WHO Classification of Primary Tumors of the Central Nervous System: a Clinician’s Opinion

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This article is devoted to the latest edition of the 2016 WHO classification of primary CNS tumors. The authors, who are clinicians and not morphologists, have tried to analyze and briefly present the main changes to the new edition of the WHO classification of primary CNS tumors, the main difference of which from the previous 2007 classification is inclusion of the molecular genetic features of primary CNS tumors in the classification criteria. The article focuses mainly on the classification issues of diffuse gliomas and glioblastoma, with assessment of the role of IDH-1,2, ATRX, TERT, and MGMT mutations as well as a 1p/19q co-deletion. The article briefly describes some new nosological forms (e.g., Grade III anaplastic pleomorphic xanthoastrocytoma) and presents a new approach to the classification of embryonic (medulloblastoma) and glial childhood tumors as well as tables of the main differences between 2016 and 2007 WHO classifications of primary CNS tumors. Based on their own clinical experience, the authors dispute with the described classification and suggest their own ideas for improving the classification of primary CNS tumors in the future.

Keywords: CNS tumors, classification, glioma, glioblastoma, medulloblastoma, IDH, MGMT, 1p/19q.

Abbreviations:

NDA — not differentiated additionally
MGMT — O6-methylguanine methyltransferase
ICD-O — the International Classification of Diseases for Oncology
RI — Research Institute
OS — overall survival
PCNST — primary central nervous system tumors
CNS — central nervous system
ATRX — the ATRX gene
EANO — European Association of Neuro-Oncology

Central nervous system tumors are neoplasms of different histological nature, malignancy, localization, and invasiveness. They can be subdivided into primary (originating from the tissues forming the meninges and the medullary substance) and metastatic tumors (distant metastases into the brain and/or spinal cord and/or their meninges caused by spread of various human malignant neoplasms). This article discusses the new edition of the 2016 WHO Classification of Primary CNS Tumors (PCNST) [1].

The questions regarding classification of PCNST have been raised since the very beginning of the era of modern neurosurgery; i.e., approximately since the early 20th century. In accordance with the general approaches to morphological classification of human tumors under the special committees under the auspices of the World Health Organization, the first expert meeting to elabo-
ics” [5]. The next edition of the classification provided by the expert committee was released in 2007, under the general editorship of Prof. D. Louis et al. [6] As the data on genetic features and heterogeneity within the previously described morphological groups of CNS tumors was being rapidly accumulated, new morphological variants were revealed, the biological aspects of tumor development in children were refined and taking into account other factors, it took a rather long time for the new edition of the WHO classification to be published. Not until 2016 was it released. The authors interpret the new edition of the WHO classification as the modified fourth edition rather than the fifth one [1, 7]. We find it important that Prof. A.G. Korshunov, who had headed the Laboratory of Neuromorphology at the Burdenko Neurosurgical Institute (over the past years, he has been working at the Laboratory of Neuromorphology of the Heidelberg University Hospital, Germany), was one of the co-authors preparing the two latest editions of the WHO classification (2007 and 2016). In the section on morphology of pediatric CNS tumors of the 2016 Classification, references are given to Dr. Med. Sci. M.M. Ryzhova, the head of the Laboratory of Neuromorphology at Burdenko Neurosurgical Institute (now known as the N.N. Burdenko National Scientific and Practical Center for Neurosurgery).

The authors, who are clinicians rather than morphologists, have done their best to analyze and summarize the main changes made to the WHO classification of primary CNS tumors in its new edition. We mean that the changes introduced to the classification are associated with a rich body of morphological and morphogenetic studies, as well as with the clinical and pathomorphological parallels, and it is not easy for a clinician to wade through this complex matter.

The overall structure of the 2016 WHO Classification of Tumors of the Central Nervous System

Like in previous editions (2000 and 2007), the classification tables showing the morphological tumor types were built in the conventional manner.

All tumors were categorized as follows:
— neuroepithelial tumors;
— peripheral nerve sheath tumors;
— meningeal tumors;
— germ-cell tumors;
— lymphoma and hematopoietic tumors;
— tumors of the sellar region.

The morphological type of a tumor is followed by:
— a 4-digit numeric code according to the International Classification of Diseases for Oncology (ICD-O, 3rd edition (2000)) [9];
— the digit (0 through 3) given after the slash is also taken from the Classification of Diseases for Oncology. However, it is not the degree of malignancy but the so-called biological behavior (see explanation in the text).

The table summarizing the degrees of tumor malignancy (“grade”) denoted with Roman numerals, I through IV, is given separately (see explanation in the text).

The first edition of the International Classification of Diseases for Oncology (ICD-O) was approved in 1969 on the basis of the American Cancer Society’s (1968) Manual of Tumor Nomenclature and Coding [8]. The most recent, 3rd edition, of ICD-O, was published in 2000 [9]. So what does the number following the slash in ICD-O mean? It is the so-called “biological behavior of a tumor” according to the following scale:

/0 — benign tumor;
/1 — it is unclear whether a tumor is benign or malignant;
/2 — non-invasive cancer;
/3 — malignant neoplasm, primary site;
/6 — malignant neoplasm, metastasis;
/9 — malignant neoplasm; there is no certainty whether it is a primary site or metastasis.

The Classification of PCNST uses only codes 0, 1, and 3 from this list.

The conception of the degree of malignancy (grade) was suggested for classifying tumors of the CNS by K. Zulch: a 5-point scale (0 though IV) was used. This scale originated from the classification proposed by J. Kernohan in 1952, where 0 stood for neuroma, meningioma, cranioopharyngioma, pituitary adenoma; IV stood for medulloblastoma and glioblastoma [10, 11].

We now turn to the 2016 WHO Classification being discussed. Identically to the previous 2000 and 2007 editions, it presents a table with Grade specified for all the tumors. However, we believe that this gradation of absolutely all CNS tumors needs revision: while gliomas can be of different degrees of malignancy, medulloblastoma can be only of grade IV. What is the reason for using this conception for the tumors that have only one variant? As for gliomas, the categorization according to Grade is a modification of the St. Anne—Mayo grading system (which, in its turn, is based on the Daumas—Duport grading system, 1988) [12]. For neuro-oncologists involved in clinical research, it is important to remember that this gradation in based on detecting the following signs in the microscopy image of a specimen prepared for morphological analysis: nuclear atypia, mitotic figures, vascular endothelial cell proliferation, and presence of necrosis. These signs are taken into account in the following way:

Grade I — none of signs is detected;
Grade II — only one of the aforementioned signs is detected (usually it is nuclear atypia but single mitotic figures are also allowed);
Grade III — many mitotic figures are detected in the tumor;
Grade IV — intense proliferation of endothelial vessels, presence of necrosis.

Summarizing the brief overview of the classification, we would like to mention that regardless of the title “Tumors of the CNS”, it also contains such sections as “Tumors of the...
peripheral nervous system" and even "Tumors of the sellar region". However, the former ones are "non-CNS tumors", while the latter ones include cranioopharyngioma, myeloid sarcoma, spindle cell oncocytoma, and pituitary tumors but exclude pituitary adenomas (pituitary adenomas are considered in the WHO classification of human endocrine tumors).

The authors of the classification were scrupulous about using the plain and italic fonts when talking about terms and diagnoses: italics can be used only for specific genes (e.g., ATRX) but not for a gene family (e.g., IDH, H3). To avoid excessive hyphenation, the hyphen is not used for the word "wildtype" but is used in some other situations (e.g., RELA fusion-positive).

The degree of malignancy (Grade) is always written in Roman numerals (I, II, III, IV) but never in Arabic ones (1, 2—4). We suggest using a number of English terms in Russian-language literature in order not to make this classification more cumbersome and not to cause potential misinterpretation of the diagnosis by different specialists.

When translating the terms to Russian, we relied upon the study by our colleagues from St. Petersburg (the well-known morphologist D.E. Matsko being the lead author), which also focused on the new 2016 WHO classification of CNS tumors.

2016 WHO classification of CNS tumors: what is new?

The key difference between the 2016 Classification and the 2007 edition is that a number of gene mutations have been included in the classification parameters. We will do our best to mention most of them, although such amendments as those made in the section devoted to pediatric cerebral tumors are worthy of an individual review.

Diffuse gliomas

According to the studies conducted in 2005—2016, the following mutations largely determining the disease prognosis were singled out from one of the most frequent groups of primary CNS tumors (neuroepithelial tumors and gliomas in particular):

- mutations in the IDH1 and IDH2 genes
- 1p/19q codeletion;
- methylation of the MGMT gene.

The IDH1 (codon 132) and IDH2 (codon 172) genes are the genes encoding isocitrate dehydrogenase, an enzyme involved in the citric acid cycle; IDH2 mutation is 10 times less frequent than IDH1 mutation and these mutations never occur simultaneously [14]. Isocitrate dehydrogenase catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate giving rise to NADPH, which, in its turn, is needed for regeneration of reduced glutathione, the key antioxidant in the cell [15]. As a result of IDH1 mutations, IDH1 enzyme partially loses its function of partaking in oxidative decarboxylation of isocitrate, while becoming able to reduce α-ketoglutarate to 2-hydroxyglutarate by consuming NADPH to yield NADP+. It has been demonstrated that the level of the oncometabolite 2-hydroxyglutarate in IDH1 mutant cells is much higher than that in cells carrying no mutations in the IDH1 gene. The exact mechanism of recruitment of 2-hydroxyglutarate in carcinogenesis is yet to be discovered. There is evidence that that 2-hydroxyglutarate inhibits α-ketoglutarate-dependent dioxygenases that are needed to ensure histone demethylation. Hence, it follows that mutations in the IDH1 gene make the cells more susceptible to gene rearrangements caused by oxidative stress, thus being the motive force of glioma development. On the other hand, tumor cells carrying IDH1 mutations become more sensitive to antitumor therapy that has a cytotoxic effect due to formation of reactive oxygen species [14, 15].

Detection of mutations in the IDH1 (codon 132) and IDH2 (codon 172) genes in most Grade II—III diffuse gliomas and in some (~10%) glioblastomas [1, 6] followed by assessment of the prognostic value of these mutations has made it possible to formulate the modern conception of "secondary glioblastoma" as a tumor originating from a less aggressive form: most likely, the tumor was originally of Grade II and then becomes Grade III. If one of these mutations is revealed in the tumor, we actually deal not with an individual low-grade glioma or an "anaplastic astrocytoma" or a "secondary glioblastoma", but with a tumor for which it took several (sometimes more than 10) years to develop. This conception is supported by the fact that these mutations are very stable: if they were detected in a patient when verifying the diagnosis for the first time (e.g., Grade II tumor), the same IDH1 or IDH2 mutation in the genes (but not both) will still be detected even many years later, upon reoperation involving morphological verification of the tumor (Grade IV). The recently published clinical studies demonstrated the overall prognostic significance of these tumor markers and the ability of tumors carrying mutations to provide a good response to chemotherapy (with both temozolomide and nitroso derivatives) and to radiation therapy; the residual tumor volume often significantly decreased after treatment [16]. Furthermore, no significant difference in the overall survival is revealed between Grade II and Grade III astrocytomas found to carry a mutation [17, 18].

Chromosomal 1p/19q codeletion in gliomas has been described a relatively long time ago. Its presence it primarily attributed to oligodendroglial tumors. The updated edition of the classification specifies that an oncologist is eligible to diagnose the patient with oligodendrogloma only if the 1p/19q codeletion was revealed. It was recommended to give up on using the term "oligoastrocytoma" [1, 6, 7]. The 1p/19q codeletion is usually accompanied by IDH1 mutation. The codeletion revealed in a CNS tumor is believed to be associated with favorable course of the disease and good response to chemotherapy [15, 19—22].
The role of methylation of the \textit{MGMT} gene in glioblastoma was described after the first large-scale international study conducted by R. Stupp et al. [23, 24], who compared radiation therapy + chemotherapy with temozolomide and radiation therapy only (without chemotherapy) as first-line postoperative treatment. Originally, the \textit{MGMT} gene status was supposed to be examined to predict the effectiveness of temozolomide chemotherapy. The \textit{MGMT} gene is responsible for the presence of \textit{MGMT} enzyme (O6-methylguanine-methyltransferase) in the tumor; this enzyme repairs DNA damage caused by alkylating agents (e.g., chemotherapeutic agents such as temozolomide and nitroso derivatives), thus impeding the action of the chemotherapeutic agent on tumor cell. The “methylated” status of the \textit{MGMT} gene means that \textit{MGMT} enzyme is not produced, DNA is not repaired, and treatment will be more effective. In some laboratories, it is not methylation of the \textit{MGMT} gene that is tested but the \textit{MGMT} expression level. In this case, the higher the expression level, the less effective therapy with alkylating agents is. It was found when studying these interactions (Table 1) that \textit{MGMT}, in addition to being a predictor of chemotherapeutic agent effectiveness, is a significant prognostic factor of survival: the overall survival is higher in patients carrying the methylated \textit{MGMT} gene than that in patient carrying the nonmethylated \textit{MGMT} gene [23].

Because of a number of reasons, including the lack of standardized methods for testing the methylation status of the \textit{MGMT} gene, chemoradiation therapy in the group of patients carrying the nonmethylated gene was reported to be somewhat more effective than radiation therapy only [23]. Finally, as long as there are no serious alternative approaches to first-line therapy of glioblastoma, the current guidelines for glioblastoma treatment (NCCN, EANO, and clinical guidelines of the Ministry of Healthcare of the Russian Federation) refer to chemoradiation therapy with temozolomide as the first-line treatment regardless of the patient’s \textit{MGMT} status.

Figure 1 shows a schematic view of the classification of diffuse gliomas.

Let us have a closer look at several mutations that were described in the section “Gliomas” in the classification under discussion: mutations in the \textit{ATRX}, \textit{TERT}, and \textit{TP53} genes.

Somatic mutations in the \textit{p53} gene occur with different frequencies in almost all tumors, including brain tumors, and are likely to be associated with poor prognosis.

The \textit{ATRX} gene resides on the X chromosome (Xq13). The protein encoded by the \textit{ATRX} gene is involved in DNA methylation and affects expression of many genes. The \textit{ATRX} mutation often occurs in astrocytic gliomas and is almost never detected in oligodendroglia; the loss of the \textit{ATRX} gene is associated with a more favorable prognosis. It was demonstrated in some studies that the presence of the \textit{ATRX} mutation in glioblastoma is associated with the so-called microsatellite instability: this DNA condition is accompanied by higher susceptibility to further mutations and, therefore, by resistance to alkylating agents (e.g., temozolomide). In this classification, testing for the \textit{ATRX} and \textit{p53} mutations is recommended to refine the diagnosis but is not an obligatory diagnostic criterion.

This is also true for the mutation in the \textit{TERT} (telomerase reverse transcriptase) gene. The association between this mutation per se and prognosis is unclear, but the following correlation with the \textit{IDH1} mutation status was revealed [14]:

- \textit{TERT} mut/\textit{IDH1} mut — the most favorable prognosis (this combination is most frequently observed for oligodendroglial tumors);
- \textit{TERT} mut/\textit{IDH1} wt — the worst survival (this combination is most frequently found in primary glioblastoma);
- \textit{TERT} wt/\textit{IDH1} mut — the appreciably high survival rate; the combination is usually found for Grade II—III diffuse astrocytoma;
- \textit{TERT} wt/\textit{IDH1} wt — it is also likely to be found in astrocytic gliomas and is associated with the moderately good prognosis.

Hence, in accordance with the requirements presented in the most recent edition of the 2016 WHO Classification of CNS Tumors, the integrated diagnosis of diffuse glioma currently includes:

- diagnosis (in accordance with how it appears in the table summarizing the diagnoses);
- Grade;
- molecular data: the \textit{IDH1},2 mutations; \textit{1p/19} codeletion, methylation of the \textit{MGMT} gene.

If testing for mutations was performed but no mutations were detected, the word “wildtype” (abbreviated form, \textit{wt}) is given next to the corresponding tested (abbreviated) mutation. If no testing for mutations was carried out for some reasons, the abbreviation "NOS" (not otherwise specified) is given; i.e., testing for one or several aforementioned mutations was not performed and the status unknown.

As compared to the 2007 edition of Classification, such terms as “protoplasmic astrocytoma” and “fibrillary astrocytoma” have been excluded, but the term “hemispheric astrocytoma” was left in the 2016 edition. The mor-

\begin{table}
\centering
\caption{Survival rates in the glioblastoma groups depending on methylation of the \textit{MGMT} gene}
\begin{tabular}{|l|c|c|}
\hline
 & Median overall survival, months & Methylated \textit{MGMT} & Non-methylated \textit{MGMT} \\
\hline
Surgery + radiation therapy & 15.7 & 11.8 \\
Surgery + radiation therapy + temozolomide & 21.7 & 12.7 \\
\hline
\end{tabular}
\end{table}
phologists attribute this to the fact that the former two entities lose their histospecificity, while hemismacrocytic astrocytoma retains its features [1, 6, 7].

The concept of "gliomatosis cerebri" was also been excluded from the most recent edition of classification. In the previous edition, this term was used to denote diffuse gliomas affecting at least three lobes of the brain or spreading around the midline cerebral structures, around the ventricular system of the brain (Fig. 2). Since the genetic profile and morphological pattern of the tumor have a more significant prognostic value than its extent of spread, it was recommended to specify the diagnosis for all the aforedescribed entries (morphological type, Grade, mutation status) [1, 7].

Here, let us engage into polemics once again. Of course, the new classification of CNS tumors being discussed in this publication is a morphological classification. In fact, it is difficult to reach perfection in classification in our field like it is for other tumor types, since the TNM classification is inapplicable, tumor size is a prognostically unfavorable factor (all other conditions being equal), but every morphology and genetics are the key prognostic factors. Yet, we are dealing with rather separable and resectable tumors is some cases, while in other cases dealing with primary multiple gliomas, or with new metachronous tumor sites in different brain regions, or with true metastases (e.g., to meninges of the brain and spinal cord) within the CNS (so far we are talking only about diffuse gliomas), etc. In this case, "gliomatosis" is the only possible term for the diffuse spread of primary infiltrating glioma to the deep portions of the cerebral hemispheres (Fig. 2), when surgical resection cannot be considered. Classification of the CNS tumors can probably be developed using the classical parameters of topographic anatomy, but on the basis of the modern neuroimaging techniques rather than using the classical parameters only.

*characteristic but not required for diagnosis

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**Fig. 1. Classification of diffuse cerebral gliomas** (reprinted with permission from D.E. Matsko et al. [13])
Glioblastoma

In the new edition of the 2016 WHO Classification, glioblastoma is classified in three main entities:

1) IDH-wt glioblastoma — accounts for ~90% of all newly diagnosed glioblastomas (also known as de novo glioblastoma) and is usually found in patients aged 55 years and older [30];

2) IDH-mut glioblastoma is found in ~10% of all newly diagnosed glioblastomas and also known as a "secondary glioblastoma"; it is most frequently found in patients of young age (but rarely in children younger than 15 years old) and can be revealed in patients diagnosed with Grade II—III diffuse astrocytoma a rather long time ago; and

3) glioblastoma, NOS when no testing for IDH1 and IDH2 mutations was carried out.

In order to understand the role played by IDH1 and IDH2 mutations in the prognosis, let us summarize the clinical data (reprinted from [1, 17]) in Table 2.

The presented data demonstrate that the overall survival of patients with glioblastoma carrying an IDH mutation (31 months) is at least twice as high as that in patients with IDH-wt glioblastoma.

Since IDH1 and IDH2 mutations are actually extremely rare in patients older than 55 years of age, the authors of the classification inferred that testing for these mutations by sequencing of specimens collected from patients of this age group might be not obligatory if negative response to immunohistochemical reagents was detected [16].

A new variant of glioblastoma (epithelioid glioblastoma) was added. This variant is IDH-wt. It is found predominantly in children and young adults, being typically located in the convex surface of the cerebral hemispheres and in the diencephalon. This tumor is often found to carry a BRAF V600E mutation [25, 26].

Other astrocytic gliomas

"Grade III anaplastic pleomorphic xanthoastrocytoma" was added to the 2016 WHO Classification of PCNST instead of the descriptive concept "pleomorphic xanthoastrocytoma with an anaplastic component" in the previous edition of classification. The criteria of malignancy are as follows: mitotic figures (5—10 per field of view) sometimes accompanied by necrosis. Grade III anaplastic pleomorphic xanthoastrocytoma has a much worse prognosis than Grade II pleomorphic xanthoastrocytoma [1, 7]. Studies focused on this rare nosological entity demonstrated that it is associated with a high frequency of BRAF V600E mutation, which is responsible for whether or not proper targeted agents can be used in case of disease progression [27]. In our opinion, either there will subsequently appear a subclassification differentiating a variant of tumor with this mutation or the mutation will be used as a diagnostic criterion of this nosological entity.

Evaluation of the degree of malignancy of pilomyxoid astrocytoma was also refined. Since this tumor is often aggressive and prone to metastasizing to the subarachnoid space, it was decided not to categorize it as Grade II (as it was done in 2007 edition) but to refine this question in the next edition of Classification as a larger body of clinical data will be available.

Pediatric CNS tumors

Pediatric diffuse gliomas were previously categorized in accordance with the same principles as diffuse gliomas in adults. It was partially related to the fact that this type of tumors is rare compared to adult gliomas. However, behavior of these tumors and their response to the conventional treatment used for adults are known to be significantly different. A large number of genetic studies focused on pediatric diffuse gliomas over the past decade, making it possible to differentiate several new entities [1, 7].

One of these entities was the revealed tumor with a K27M mutation in histone H3 of the H3F3A gene or, less frequently, in histone 1 of the H3B gene. This feature was detected in diffuse midline gliomas (e.g., tumors located in the thalamus, the midbrain, and other brainstem regions, and in the craniospinal junction between the brainstem and the spinal cord). This tumor entity is more likely to occur in children and, less frequently, in young adults. Hence, the diagnosis "diffuse midline glioma, H3-K27M mutant" has been formulated, which was differentiated from the overall diagnosis "diffuse infiltrat-
ing pontine glioma” [28]. A therapeutic hope is for targeted therapy of these tumors.

The classification of medulloblastomas has been significantly changed. It is enough to have a look at the table summarizing the suggested morphological diagnoses (Table 3) to get an overview how important genetic testing in making an integrated diagnosis of this tumor currently is.

In accordance with the new classification, diagnosing one with medulloblastoma requires conducting seven immunohistochemical assays using antibodies (catenin, P75-NGFR, Gab1, Yaq1, Obx2, NeuN, P53) and two FISH assays (to identify the status of the MYC and MYCN genes). The 2016 WHO Classification of CNS Tumors under discussion also recommended the kits for conducting these tests (probably so that unified data could be obtained in different laboratories worldwide). As we are not morphologists, we will refrain from digging too much into the process of conducting these analyses [1, 7]. These data are presented only to emphasize how important the work done by neuropathologists in neuro-oncology is and how difficult their profession is, as well as to highlight the large number of tests needed to make a diagnosis.

To sum up the brief overview of the changes made in the previous classification of pediatric CNS tumors and embryonic tumors in particular, let us mention that several new nosological entities have been suggested (e.g., CNS embryonal tumor with rhabdoid features and embryonal tumor with multilayered rosettes, C19MC-altered). Furthermore, a decision was made to remove the term "primitive neuroectodermal tumor" (PNET). Instead of using the latter term, it was suggested that either the tumor entity is specified by conducting a number of genetic assays or the term "NOS" (or the term suggested by our colleagues from St. Petersburg, D.E. Matsko et al [13], NDA — not differentiated additionally) is used [13]: for example, "embryonal tumor with multilayered rosettes, NOS".

Summary of the changes made in the 2016 Classification

To sum up our contemplations on the new 2016 WHO Classification of CNS Tumors, we would like to list the key aspects in which it differs from the previous edition (2007):

— the concept and structure of CNS tumor diagnoses in the molecular era was formulated;
— restructuring was made for diffuse gliomas, medulloblastomas, and other embryonal tumors, with incorporation of genetically defined entities and removing the term "primitive neuroectodermal tumor" (PNET);
— new terms, variants, and entities were added:
  — IDH wt and IDH mut glioblastoma;
  — epithelioid glioblastoma;
  — diffuse leptomeningeal glioneuronal tumor;
  — anaplastic pleomorphic xanthoastrocytoma;
  — diffuse midline glioma, H3 K27M mutant;
  — embryonal tumor with multilayered rosettes, C19MC-altered;
  — ependymoma, RELA fusion-positive;
  — glioblastoma with primitive neuronal component;
  — multinodular and vacuolated pattern of ganglion cell tumor;
— the previous variants and entities were deleted:
  — gliomatosis cerebri;
  — protoplasmic and fibrillary astrocytoma variants;
  — cellular ependymoma variant;
— the terms "primitive neuroectodermal tumor", "primitive neuroectodermal tumor" (PNET);
— a new approach to differentiating pediatric tumors of similar morphology using new, genetically defined signs was suggested;
— brain invasion was added as a diagnostic criterion for atypical meningioma;
— solitary fibrous tumor and hemangiopericytoma were classified into one SFT/HPC group and the Grade system was adapted for this tumor;
— the term "hybrid nerve sheath tumor" was added; the melanotic schwannoma was separated from other schwannomas;
— the entities included in hematopoietic/lymphoid tumors of the CNS were expanded.

If one would like to study the new classification in more detail, we suggest reading the publication by our colleagues from St. Petersburg, D.E. Matsko et al [13], which has already been cited in this review, and the papers by foreign authors focused on the new classification in general [1, 7, 29] as well as on its different sections, such as meningiomas [30], pediatric diffuse gliomas [28], medulloblastomas [31], etc.

Conclusions: the questions for discussion about the 2016 WHO Classification of CNS Tumors.

We have already presented our considerations in the text above. Now let us dwell on some other aspects.

Our rather vast clinical experience gives grounds for assuming that Grade II IDH1,2-wt diffuse gliomas require need to be further subclassified. We mean that these gliomas were referred to as "glioblastoma-like" tumors in a number of publications focused on IDH1 and IDH2 mutations, since they typically are more progredient than mutant gliomas. Nevertheless, our experience demon-

### Table 2. Survival rates in the glioblastoma groups depending on presence of mutations in the IDH gene

<table>
<thead>
<tr>
<th>Survival endpoint</th>
<th>IDH-wt</th>
<th>IDH-mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival, months</td>
<td>9.9</td>
<td>24</td>
</tr>
<tr>
<td>Surgery + radiation therapy</td>
<td>15</td>
<td>31</td>
</tr>
</tbody>
</table>

*Table 2. Survival rates in the glioblastoma groups depending on presence of mutations in the IDH gene.*
strates that some of these tumors are progressing very slowly (for as long as several years). Therefore, most probably, the refining genetic differences within this glioma subgroup are yet to be elucidated. On the other hand, when these tumors progress and their degree of malignancy increases and eventually become a glioblastoma as evaluated using the aforesaid criteria for determining tumor grade, is not this tumor a secondary glioblastoma in this case? It turns out that it is; however, how can this secondary glioblastoma be differentiated from glioblastoma secondary with respect to its IDHI (or IDH2) mutation status?

Some subclassifications seem to be rather morphogenetic when it comes to the genetic signs, since they are not supported by difference in prognosis and treatment response. For some of these new nosological entities, it has been reported that a certain target therapy can potentially be developed. Meanwhile, some of the other nosological entities have never been reported. For example, even today, detection of the BRAF V600E mutation in some glioma entities (pilocytic astrocytoma, ganglioglioma, anaplastic pleomorphic xanthoastrocytoma, etc.) allows the oncologists to prescribe targeted therapies (vemurafenib, dabrafenib) in complex clinical cases, and the desired outcome is achieved: the tumor nidus decreases in size and the clinical symptoms improve. Discontinuation of corticosteroid therapy can be recommended in some cases. However, this was not mentioned in the classification, probably because of the lack of data. But then it is too early to talk about other targeted therapy approaches (e.g., treating medulloblastoma, SSH mut with a target drug) until proper data are accumulated.

After we have thoroughly studied the new edition of 2016 WHO Classification of Tumors of the Central Nervous System, most of our questions are addressed to ourselves. Today, in order to make an integrated morphogenetic diagnosis of a CNS tumor, the following conditions need to be met:

— there should be an expert laboratory with highly experienced staff (neuromorphologists, laboratory scientists, and, ideally, a geneticist);
— the laboratory should be equipped with proper facilities and components for conducting a broad range of high-tech tests (mentioned earlier in the text);
— the laboratory should allow performing clinical morphogenetic studies and potentially the clinical morpho-neuroimaging studies to further investigate the pressing issues related to classification of CNS tumors.

Unfortunately, too few laboratories in Russia meet these criteria. It is good that such laboratories are being established gradually. Along with the laboratory at our center (the N.N. Burdenko National Scientific and Practical Center for Neurosurgery), there are ones at the Institute of Roentgenoradiology, N.N. Petrov Research Institute of Oncology (Ministry of Healthcare of the Russian Federation, St. Petersburg, Russia) and the laboratory in Novosibirsk (E.I. Voronina).

Authors declare no conflict of interest.

REFERENCES


Table 3. Alternative variants for medulloblastoma in the 2016 WHO Classification of Tumors of the CNS

| Medulloblastoma, histologically defined |
| Medulloblastoma, classic |
| Medulloblastoma, desmoplastic/nodular |
| Medulloblastoma with extensive nodularity |
| Medulloblastoma, large cell/anaplastic |
| Medulloblastoma, genetically defined |
| Medulloblastoma, WNT activated |
| Medulloblastoma, SHH activated, TP53 mutant |
| Medulloblastoma, SHH activated, TP53 wildtype |
| Medulloblastoma, non-WNT/non-SHH |
| Medulloblastoma, group 3 |
| Medulloblastoma, group 4 |
| Medulloblastoma, NOS |


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Anterior interbody fusion with vertebral body replacement devices (VBRDs) is currently one of the most effective methods to restore the sagittal balance and stabilize the operated functional spinal unit upon reconstructive and restorative surgery of the anterior and middle spinal columns [1].

Spine surgeons have a broad range of implants with different design at their disposal [2]. The VBRDs used in clinical practice are far from perfect. Hence, they have not only positive but also negative characteristics affecting their performance.

The objective of this study was to classify the implants for anterior interbody fusion depending on their design and functional capabilities to optimize the choice of VBRDs in reconstructive spine surgery.

**Material and Methods.** We analyzed information provided in advertising brochures, annotations, and communications describing the designs of vertebral body endoprostheses.

To study the design features of various implants, we selected 25 implant types with the structural designs of major units typical of vertebral body replacement systems. We performed static tests of mechanical features of anterior interbody fusion systems using special equipment and mathematical modeling based on the finite element technique to determine features of the stressed-deformed state in replacement of the vertebral bodies with artificial implants of various designs.

Results and Discussion. The analysis results define the prerogative of combined telescopic designs with axisymmetric accommodation of compression stresses, which enable reconstruction and stabilization of the spinal motion segment without additional fixation by a ventral plate. The classification of endoprostheses enables evaluation of advantages and disadvantages of various implants to objectively assess the mechanisms of potential postoperative complications and to prevent them. The presented data may facilitate the optimal choice of an implant with allowance for the peculiarities of a clinical situation in each particular case.

**Keywords:** spinal diseases and injuries, surgical treatment, classification of implants for anterior fusion.

To study the specific features of the design of various implants, we selected 25 types of VBRDs with the design of major components being typical of vertebral body replacement systems. The information presented in advertising booklets, annotations, and reports on the websites of the companies manufacturing the instrumentation was additionally analyzed.

In order to determine the features of stress-deformed state upon replacement of vertebral bodies with artificial implants of different design, we conducted static tests of the mechanical properties of the anterior interbody fusion implants using specialized equipment (Verification Certificate of an experimental setup R-0.5 no. 21/1701) and mathematical modeling using the finite element method.

**Results and Discussion**

Tasks to be solved by applying VBRDs are as follows:

1. **Reconstruction.** Reconstruction and restoration of the normal physiological dimensions of a functional spinal unit to correct the sagittal balance. The implanted vertebral body replacement implants need to have a certain size depending on the dimensions of a bone defect formed after corpectomy or vertebral body resection.

One of the defining characteristics of the instrumentation systems is whether or it is possible to adjust the implant height. According to this parameter, the implants can be classified as follows:

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One of the defining characteristics of the instrumentation systems is whether or it is possible to adjust the implant height. According to this parameter, the implants can be classified as follows:
1. Fixed-height monolithic implant

One of the drawbacks of these instrumentation systems is that it is impossible to correct the height of the operated functional spinal unit in a dosed manner, since a large combination of implants of different types and sizes is needed in each specific case to fill the defect between the vertebral bodies adjacent to the resected vertebra [3].

2. Monolithic implant with intraoperatively adjustable height

When using these VBRDs, a surgeon can face the problem of determining their optimal size. One needs to take into account that the resulting instrumentation is a monolithic implant with a fixed size determined by the surgeon [4].

The error in determining the implant height leads to either of two situations:

(a) if a VBRD is longer than the required size, the stress caused by compressive load on a function spinal unit in the "metal–vertebral body" system will be high, thus accelerating bone tissue resorption and increasing the risk of implant migration into the vertebral bodies [5];

(b) if a VBRD is shorter than the required size, the attempt to restore the sagittal balance will fail as no proper segment reclination will be achieved. The lack of implant stability in the interbody space will make it mobile.

The imbalance in load distribution in certain regions of the "implant–vertebral body" system in various functional positions of the operated functional spinal unit will be intermittent, thus causing endplate degradation and increasing the risk of implant migration [6].

3. Expandable instrumentation systems

Today, these systems can be regarded as most effective and perfect in restoring the anterior spinal column. They optimize sagittal balance correction as it is possible to adjust the distance between the vertebrae adjacent to the resected ones in a dosed manner. It is the key advantage of these systems, which allows one to maximally implement the tasks being set.

II. Stabilization. Rigid fixation of the operated functional spinal unit to ensure proper conditions for adequate bone block formation is an integral stage of any surgical intervention related to partial or radical resection of vertebral bodies or their fragments. The VBRDs can be subdivided into two types according to their stabilizing potential in reconstruction of a functional spinal unit.

Type A — the instrumentation intended for reconstructing the functional spinal unit. The stabilizing potential of these systems is insufficient for maintaining the intraoperative correction of the sagittal balance. When using them, the functional spinal unit needs to be fixed with ventral plates or transpedicular systems.

Type B — the instrumentation systems that allow one to reconstruct and stabilize the functional spinal unit without additional ventral plate fixation [7, 8].

These implants are characterized by the following features:

— they reduce the risk of injury associated with the intervention;

— they allow a surgeon to solve the tasks set through a single approach and using a single instrumentation system;

— they are less metal-consuming compared to type A implants and additional stabilization systems, thus being lightweight;

— they reduce the duration and net cost of the instrumentation stage during the surgery.

III. Ensuring the conditions for bone block formation

Metal implants have proved effective upon intraoperative correction of the sagittal balance. However, the frequency of postoperative complications caused by migration of the instrumentation systems remains rather high (3—13%) [9]. This can be attributed to degradation (punching out) of bone structures of the vertebral bodies because of the difference in the Young's moduli of the bone tissue and the metal under high pressure from the butt-end surface of the cages on vertebral endplates, as well as to osteolysis and accelerated resorption of bone tissue in the "bone tissue—implant" system.

Bony union of the vertebrae in the operated functional spinal unit needs to be achieved to maintain the existing sagittal balance correction. In this connection, ensuring the conditions for bone block formation in the implant insertion zone is one of the key characteristics of VBRDs. Meanwhile, some available instrumentation systems do not ensure formation of effective regenerated bone because the volume of the hollow core filled with autobone or bone substitute material is insufficient and because proper contact between the filler and vertebral endplates is not achieved. The signs of failed anterior intervertebral fusion are often an indication for reoperation and can develop both in the short- and long-term postoperative period [10, 11].

The design characteristics of both monolithic and expandable instrumentation systems are responsible for the level of their functional capabilities [12, 13].

According to their function (i.e., the scope and efficiency of solving the tasks set), the instrumentation systems can be divided into four groups.

I. Vertebral body replacement devices with the reconstruction function. Some features of the instrumentation systems ADD, Obelisc, TeCorp, Tellur, XMESH, XRL, Xpand, XPAND-R, GIZA, VBR-Actipore, ECD, Hydrolift, and Synex System limit their effectiveness in ensuring the conditions for fusion of the vertebrae in an operated functional spinal unit (Fig. 1).

Let us consider ADD as an example. This implant is convenient to be used and can be used without any additional tools (retractors). However, its telescopic mecha-
nism is located inside the device, thus reducing the volume of the hollow core that can be filled with a bio- or a composite material.

We believe that the implants classified into this group are sufficiently effective to be used as a reclination system. Additional stabilization of one or several functional spinal unit(s) with ventral plates or transpedicular systems needs to be performed when using them.

II. Instrumentation systems with the "reconstruction + stabilization" function. The ADDplus, BodyVertEx, Monolit, and FORTIFYI implants have a broad range of functional characteristics as they allow achieving the de-
sired reclusion and stabilization of the functional spinal unit. In other words, they simultaneously act as type A systems and as ventral plates.

III. Instrumentation systems with the "reconstruction + hollow core for the material" function. The hollow core to be filled with a filling material in monolithic systems is definitely larger than that in the expandable ones. From this perspective, expandable implants X-tenz, VERTE-SPAN, VBR, and VLIFT are the ones being most similar to the Mesh system (Fig. 2).

They have a reconstruction function and provide conditions for vertebral fusion. It is noteworthy that the volume of the hollow core for the filler in expandable VBRDs depends on design characteristics of the implant (i.e., on their total volume and on the volume occupied by the telescopic mechanism). These implants are used in combination with additional stabilization systems, such as ventral plates or transpedicular systems.

IV. Instrumentation systems with the "reconstruction + stabilization + conditions for bone block formation" function. VBRDs belonging to this group have a combination of design characteristics that maximally enhance the clinical effectiveness of anterior interbody fusion with metal fixation. These systems are effective when used for reconstruction and stabilization of the operated functional spinal unit and make formation of the supporting bone block possible as the hollow core for a filler (autobone or bone substitute material) is large enough. The TPS implant ensuring the maximum contact area in the "metal—bone" and "material—bone" systems comes under notice (Fig. 3).

After insertion of this system into a bone defect and reclusion of the functional spinal unit, its design allows compaction of the material in the zone where it contacts the vertebral body. However, the substantially large orifices on the lateral surfaces may make it difficult to tightly pack the hollow core with material (fragmented autobone or bone substitute material). This implant is an implant with discrete distribution of compression load. When it comes to load distribution, the axisymmetric systems (VBR) are more effective and reliable than TPS systems due to the uniform load distribution. As opposed to the VBR systems, these cages are heavier, more metal-consuming and more difficult to manufacture, which increases their net cost and makes them less accessible for patients.

Such implants as ADD, ADDplus, BodyVertEx, TeCorp, Monolit, and ECD, are used for anterior interbody fusion with metal fixation at the level of cervical spine. The volume of the hollow core for the filler is smaller than that in the Mech implant and VERTE-SPAN, VBR, and VLIFT expandable systems. Furthermore, tightness of the contact between the VBRD filler and bone structures of the reconstructed vertebral body cannot be increased in such implants as ADD, ADDplus, BodyVertEx, TeCorp, Monolit, and ECD.

We analyzed the design characteristics of the cages used for anterior interbody fusion with metal fixation at the level of cervical spine. A vertical cylindrical expandable mesh vertebral body replacement device (LAS) was designed (Fig. 4). The implant was designed according to the results of computer and mathematical modeling to identify the rational characteristics of the cages and their effect on functional parameters of the implants. The optimal configuration of the implant was developed with allowance for the anatomical and biomechanical features of the cervical spine, physical properties of bone tissue,
cage filler, implant material, as well as technical, functional, and mechanical characteristics of the system.

The implant was classified as a type B system (hybrid VBRDs) and requires no additional ventral plate stabilization. The volume of the hollow core for the filler material is rather large, making the implant more similar to hollow cylindrical mesh cages (Mech) in terms of this parameter. The implant is classified as a system with axisymmetric distribution of compressive stress so it is lightweight. In order to reduce the number of constituent elements and weight and to make the implant easier to manufacture, the method of deformation-induced thread lock (instead of screw locks) was developed to maintain the proper position of metal implants for anterior intervertebral fusion with metal fixation. The orifice diameter and their arrangement in the implant semi-housing allow packing some additional filler material and compacting it directly in the area where the implant contacts the endplates of the vertebrae adjacent to the operated one.

The proposed classification for design characteristics and functional capabilities of vertebral body replacement devices makes it possible to choose the optimal instrumentation system among the plethora of marketed vertebral body replacement implants.

**Conclusions**

The analysis of performance characteristics of VBRDs for anterior interbody fusion allows one to classify the vertebral body replacement devices into four groups depending on the range of tasks set and the effectiveness of these implants in reconstructive interventions on the anterior and middle spinal columns.

In our opinion, this classification allows one to assess the advantages and drawbacks of various implants in order to make an unbiased evaluation of the mechanisms of development of potential postoperative complications and to prevent them. These data can help making the optimal choice of an instrumentation system with allowance for the features of the clinical situation in each particular case.

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Nasal liquorrhea is cerebrospinal fluid leakage from cerebrospinal fluid spaces of the cerebral cavity into the nasal cavity or paranasal sinuses due to congenital or acquired abnormalities of the skull base bones and meninges of various etiologies. The severity of liquorrhea varies from hidden manifestations to profuse leakage of cerebrospinal fluid from the nasal cavity. The diagnosis of overt nasal liquorrhea is not problematic, but the diagnosis of latent liquorrhea is a challenge. In this case, the disease leads to potentially fatal complications, such as meningitis (the risk amounts to 10—37%), pneumocephalus, pneumonia, etc. These peculiarities give rise to two main tasks: early diagnosis confirming liquorrhea and accurate identification of the CSF fistula location when planning further surgical management.

**Purpose** — the study purpose was to review and comparatively analyze all modern methods of diagnosing nasal liquorrhea as well as to substantiate the most effective and promising approaches and algorithms.

**Material and methods.** The study included papers in English and Russian found in the Pubmed database and related to the diagnosis of basal liquorrhea of different etiology and localization.

**Results.** This review demonstrates that diagnostic tests vary widely in sensitivity, specificity, accuracy, invasiveness, and cost. Given all the criteria, detection of beta-2-transferrin or beta-trace protein is the best method for confirming nasal liquorrhea, and high-resolution computed tomography is the best technique for localization of the abnormality.

**Conclusion.** Based on the review, we suggest a diagnostic algorithm for nasal liquorrhea. However, the evidence presented in this review is unfortunately not very reliable, which indicates the existing need for more accurate studies.

**Keywords:** nasal liquorrhea, double ring sign, glucose test, beta-2-transferrin, beta-trace protein, high-resolution CT, CT cisternography, MRI cisternography, radionuclide cisternography, fluorescein test.

CSF rhinorrhea is leak of cerebrospinal fluid (CSF) from the cerebrospinal fluid spaces in the cerebral cavity into the nasal cavity or paranasal sinuses due to congenital or acquired abnormalities of the skull base bones and meninges of various etiologies. The causes of its development include traumatic brain injury (traumatic liquorrhea), endoscopic and neurosurgical interventions (iatrogenic liquorrhea). Liquorrhea can also be idiopathic (spontaneous CSF rhinorrhea): in this case, it is often related to increased intracranial pressure [1].

The severity of CSF rhinorrhea varies from hidden manifestations to profuse CSF leak from the nasal cavity. The diagnosis of overt CSF rhinorrhea is not problematic, but the diagnosis of hidden liquorrhea is a challenge. In this case, the disease leads to potentially fatal complications, such as meningitis (the risk amounting to 10—37%), pneumocephalus, pneumonia, etc. The mortality rate is 8—10% [2]. These peculiarities give rise to two main objectives: early diagnosis confirming liquorrhea and accurate identification of the CSF fistula location when planning further surgical management. It has been demonstrated that the inability to identify precise location of the defect may lead to surgery failure [3]. The methods used to confirm the diagnosis of CSF rhinorrhea include visual examination, the ring sign, the glucose test, and tests to detect beta-2-transferrin and beta-trace protein in secreted fluid, as well as radionuclide cisternography. High-resolution CT (HRCT), MR cisternography (MRC), CT cisternography, endoscopic endonasal examination, and fluorescein test are used to identify precise location of the defect. These methods differ in their sensitivity, specificity, accuracy, availability, cost, and invasiveness.

The objective of this study was to review and comparatively analyze all the modern methods for diagnosing CSF rhinorrhea, as well as to substantiate the most effective and promising approaches and algorithms.

**Materials and Methods**

The review focused on publications in English and Russian languages retrieved from the Pubmed database.
and related to the diagnosis of basal liquorrea of different etiology and localization. A total of 47 publications were selected. The sensitivity, specificity, and accuracy of nine methods used to diagnose CSF rhinorrea were analyzed.

Results

Visual examination, the ring sign. If the accurately collected medical history and patient’s complaints give grounds to suspect CSF rhinorrea, visual examination involving nasal vasconstriction and forward flexion of the head is performed. Either weak or strong leaking of clear and colorless fluid may be indicative of overt CSF rhinorrea. Differential diagnosis should be made between CSF rhinorrea and allergic or vasomotor rhinitis, or postoperative condition following rhinosurgery. When CSF is mixed with blood, a typical light-yellow halo sign appears around the central blood spot on gauze or bed linens [4]. This ring sign used to be considered the earliest symptom of traumatic CSF rhinorrea. We found only one study focusing on this method. D. Dula and W. Fales [5] mixed one drop of blood with either CSF, saline, tap water, or rhinorrea fluid; different concentrations of blood and CSF were tested. The resulting combinations were placed onto various white materials (standard laboratory filter paper, coffee filters, bed linens, paper towels). They found that when mixed with blood, CSF at concentration of 30—90% always gave rise to a ring sign. However, when blood was mixed with other clear fluids, the ring sign also remained on all the tested filter surfaces, thus indicating that this test is not specific.

Determining glucose level in the nasal discharge (the glucose test). In 1948, N.S. Blagoveshchenskaya [6] suggested using a biochemical analysis to determine glucose level in the nasal discharge. Glucose concentration in CSF is known to be approximately twice as low as that in blood. Normal glucose concentration in CSF is 2.2—3.9 mmol/L, which is higher than that in the normal nasal discharge or lacrimal fluid. This laboratory method has conventionally been regarded as a screening test in diagnosing CSF rhinorrea because of the opinion that the presence of CSF yields positive results of the glucose test. This assumption has been disputed over the past several decades. Searching across the Pubmed database revealed 5 studies focused on this topic. D. Steedman and M. Gordon [7] examined 50 healthy volunteers and detected glucose in nasal and lacrimal secretion in 26% of them. D. Chan et al. [8] used glucose test strips in 15 individuals having CSF rhinorrea and otorrhea. They found that glucose test strips have zero specificity and low sensitivity (80%) as compared to beta-2-transferrin analysis. A. Warnacke et al. [9] retrospectively analyzed the results of using glucose test strips in 19 patients. In their study, sensitivity and specificity of the method was 100 and 45%, respectively, compared to the results obtained using beta-2 transferrin test.

A number of publications demonstrated that glucose can also be detected in nasal discharge among patients with a different pathology. These studies were started as early as in the 1960s. B. Philips et al. [10] evaluated glucose level in the upper respiratory tract secretions in 19 healthy volunteers, 20 patients with acute rhinitis, 24 patients with diabetes mellitus, and 60 patients admitted to a general adult intensive care unit. They found that nasal glucose was undetectable in healthy volunteers and detected in 50% of patients with acute rhinitis, 90% of patients with diabetes mellitus, and 52% of ventilated patients on ICU. The conclusion drawn in this study was that although glucose is not normally present in airway secretions, it appears where hyperglycemia or acute inflammation occurs. Both these pathological mechanisms are present in case of severe TBI involving skull base damage. D. Wood et al. [11] evaluated 30 healthy volunteers before and after the glucose challenge test. Hyperglycemia was induced by 20% dextrose intravenous infusion or 75 g oral glucose load. The researchers found that glucose appeared in the nasal secretion at a blood glucose level of 6.7—9.7 mmol/L, and these changes took place within 10 min.

Considering these data, it is fair to say that glucose detection in nasal discharge in patients with suspected CSF rhinorrea can be used as a diagnostic technique if it is known that a sample does not contain blood, the patient has normal blood level of glucose and has no signs of viral upper respiratory tract infection. Since these criteria are difficult to match, especially in patients with traumatic or iatrogenic liquorrea and in seriously ill patients, the risk of false-positive results is rather high, which can lead to unjustified surgical intervention.

Beta-2 transferrin test. Beta-2 transferrin and beta-trace protein are specific proteins synthesized by pial cells and the vascular plexi. The test to quantify the level of these glycoproteins in the nasal discharge is the “gold standard” in laboratory diagnosing of liquorrea in the USA and European countries. Quantification of beta-2 transferrin or beta-trace protein allows prompt, non-invasive diagnosis of basal liquorrea with high specificity and sensitivity; however, this method does not confine this defect to the skull base.

We found five studies focused on beta-2 transferrin test among the world’s published literature. A. Warnacke et al. [9] conducted beta-2 transferrin tests in 205 patients with suspected CSF rhinorrea and oto-liquorrea. They reported sensitivity and specificity of this method to be 97 and 99%, respectively, so the test was recommended as a primary screening tool for the potential CSF rhinorrea.

The other studies [12—17] were aimed at identifying the accuracy of the results of beta-2 transferrin test compared to other methods. Various techniques have been employed to conduct this test, including isoelectric fo-
cusing, immunofixation, and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) with Western blotting analysis. Regardless of the technique used for testing, the sensitivity range was 87—100% and the specificity range was 71—100%.

In two studies, T. Gorogh et al. [12] and C. McCudden et al. [13] compared the accuracy of beta-2 transferrin tests for the samples obtained from patients with CSF rhinorrhea and those from healthy volunteers. These studies involved a large number of participants (63 and 241) in study groups. Similarly, the main objective of the studies conducted by A. Marshall et al. [14] and J. Zapalac et al. [15] was to demonstrate the simplified algorithms for diagnosis and treatment of CSF rhinorrhea, including the beta-2 transferrin test. A. Marshall et al. [14] reported that 18 out of 30 patients with CSF rhinorrhea had undergone beta-2 transferrin test and all the results were positive. These findings were verified by intraoperative imaging, fluorescein test, and HRCT. J. Zapalac et al. [15] retrospectively analyzed the diagnosing and management of patients with CSF rhinorrhea. The beta-2 transferrin test showed 98% sensitivity in 44 cases.

All the authors highlighted that this diagnostic method was rather simple to be performed: the nasal secretion is collected into a tube and sent to a laboratory for testing. If secretion is scanty, the material can be collected during several days. B. Bleier et al. [16] evaluated the reliability of beta-2 transferrin test in CSF samples collected from 6 patients, either refrigerated or stored at room temperature for 7 days. Neither temperature nor storage duration was found to significantly affect test accuracy.

In all these studies, the results of beta-2 transferrin test were compared to the results of other methods, such as fluorescein test or radionuclide cisternography, and medical records were analyzed. This made it possible to reliably evaluate the accuracy of the method. Taking into account the non-invasiveness and the relatively low cost of beta-2 transferrin test, its high sensitivity and specificity observed in many cases make it a very reliable and economically sound test to verify CSF rhinorrhea [12—17].

Beta-trace protein test. M.S. Makhmuryan et al. [18] mentioned in their article that Felneghauer et al. were first to use this protein as a marker for liquororrhea, since its level in CSF is 35 times higher than that in blood. The protein is produced by the meninges, the choroidal plexi, and, to a smaller extent, by astrocytes. However, its physiological role has not been completely studied. The Pubmed database contains five publications focused on diagnosis of basal liquororrhea using the beta-trace protein test. The sensitivity and specificity of the method reported in these studies are 91—100 and 86—100%, respectively [12, 19—22]. In his study (22 cases), C. McCudden [13] reported that sensitivity and specificity of the beta-trace protein test (87 and 100%, respectively) are higher than those of the beta-2 transferrin test (71 and 94%, respectively). However, beta-trace protein is found not only in CSF but also in blood, although at extremely low concentrations. C. Meco et al. [19] reported that kidney failure increases and bacterial meningitis reduces the beta-trace protein level, so the test is not recommended for patients with these conditions. Schnabel et al. [21] also mentioned that this method has a higher sensitivity compared to the beta-2 transferrin test. Low cost and rapid data processing (the analysis takes < 15 min) are additional advantages of the test [22—24].

Although the beta-trace protein test is not used in the USA, these studies demonstrate that it is worthy of consideration as a screening method. In Russia, the beta-2 transferrin and beta-trace protein tests have so far been unavailable in clinical practice and no studies to evaluate them have been performed.

**Radionuclide cisternography.** Radionuclide cisternography is an invasive radiographic method with endolumbar administration of serum albumin tagged with radioactive iodine, radioactive phosphorus, radioactive gold, and technetium pertechnenate [23]. The distribution of these elements in the submeningeal space of the spinal cord and the brain is then evaluated in a gamma chamber. This method verifies the diagnosis of CSF rhinorrhea but does not allow one to identify defect location. Radionuclide cisternography used to be the most common method to diagnose CSF fistulae before CT and MRI were developed [24]. Today, this method is almost never used because of its poor effectiveness, high cost, and various complications; in addition, it is invasive and radioactive [25].

Three more studies dealt with using radionuclide cisternography to diagnose CSF rhinorrhea. They demonstrated that the sensitivity of this method lies in the range of 76—100%; specificity and accuracy are 100 and 90%, respectively [26—28]. Hence, this method is expensive, invasive, and has a lower sensitivity than beta-2 transferrin test.

According to these data, radionuclide cisternography is not recommended for routine verification of CSF rhinorrhea.

**High-resolution CT.** Computed tomography, a non-invasive examination technique, was designed by G. Hounsfield and A. Cormack in 1972. HRCT is the method of choice to identify the location of an osseous defect with an CSF fistula. It also provides information about the individual anatomy of each patient and allows the surgeon to plan the surgical approach (Fig. 1).

For this review, we have analyzed 7 publications meeting the inclusion criteria. It was reported in all these studies [29—35] that HRCT is the main method for identifying defect location. According to different reports, its sensitivity and specificity are 44—100 and 45—100%, respectively; the accuracy is 87—93%. In most studies, these values lay in the upper section of the 100% scale.

M. Tahir et al. [29] and M. Eljamel et al. [30] reported that HRCT had low sensitivity (43 and 48%, respectively) and specificity (45%). However, M. Tahir et
al. [29] also mentioned that HRCT is hardly available in Pakistan. Therefore, judging from the data reported by these researchers, it is unclear whether they used HRCT or just the conventional CT. M. Eljamel et al. [30] reported that examination of patients with hidden liquorrhea yielded 9.5% false-positive and 67% false-negative results. They considered a visible osseous defect, sinus wall fracture, and signs of pneumocephalus to be a positive sign according to the HRCT data.

M. Sillers et al. [31] also reported that the detection rate of CSF fistulae according to the HRCT was low (62%); all further findings in CT were verified surgically in 100% of cases. This can possibly be attributed to the fact that the study mainly involved patients with closed-head TBI and patients after endoscopic paranasal sinus surgery. In other words, they had minor defects rather than obvious skull base fractures. In some cases, HRCT allows one to detect not only the skull fractures but also CSF leak through a defect.

R. Manes et al. [32] followed up 15 patients with spontaneous CSF rhinorrhea after their HRCT findings were negative. The authors found that these 15 patients with an unclear osseous defect had opacification of the fistula in the cribriform plate, which was subsequently verified intraoperatively in 100% of cases.

Six out of eight studies aimed at evaluating the sensitivity of HRCT reported that the method had sensitivity >80% [31—35]. In one of these articles [33], the authors mentioned that sensitivity was as high as 73—87% depending on liquorrhea localization.

V. La Fata et al. [33] reported that the accuracy of determining the defect size inversely correlates with thickness of HRCT sections. If HRCT images are taken with a "step" of ~2 mm, the defect size is determined with 75% accuracy.

According to J. Stone et al. [34], the accuracy of HRCT was 100% (21 out of 21 cases verified intraoperatively). M. Gretchen et al. [35] reported the accuracy of this method to be 87%. Hence, these data allow one to infer that HRCT is more sensitive and less expensive compared to MR or CT cisternography.

It is noteworthy that HRCT can normally reveal skull base regions suspected of having a defect, but not all defects cause liquorrhea. Because of lack of specificity, a combination of CT and MRI is recommended to be used in some studies [36]. In this case, the sensitivity and accuracy of a combination of the methods is 90—96%.

Although the published data are rather controversial, HRCT is the best technique to detect the defect, to identify the features of the anatomy of the nasal cavity and paranasal sinuses, and to plan endoscopic surgery for the skull base.

**Magnetic resonance cisternography.** MR cisternography is a non-invasive imaging method used for diagnosing CSF rhinorrhea, since the signal from CSF in T2-weighted images is hyperintense. Because the image does not show the signal from osseous structures, this method yields little information about small-size CSF fistulae (<3 mm in size) but provides better identification of meningoencephalocele (Fig. 2).

We have found 7 studies discussing the role of MR cisternography in diagnosing liquorrhea. The sensitivity of this method reported by different authors [35—38] is 56—94%; specificity, 57—100%; and accuracy, 78—96%.

M. Gretchen et al. [35] recommended using MR cisternography only if HRCT provides little information as the cost of MR cisternography is high. Other authors [35, 37] recommended using a combination of these two methods, since this improves the resulting accuracy (92—100%).

Contrast-enhanced MR cisternography, with endolumbar administration of gadolinium as a contrast agent, has been described in many studies. Although this method is invasive, unlike the conventional MR cisternography, some authors [40, 41] consider it a safe and effective option to identify the location of a CSF fistula. According to their findings, sensitivity and specificity of gadolinium-enhanced MR cisternography are 61—100% and 66—80%, respectively.

Two of these studies evaluated safety of the technique. The patients were subjected to neurological examination during infusion of the contrast agent and during the follow-up period for several months. Subdural infusion of the contrast agent can cause such complications as an allergic response, neurological symptoms, an epileptic seizure, and cerebrovascular disturbance. These complications were documented in none of the studies, except for headache (24% of patients), which was eliminated by conservative treatment [37, 42].

![Fig. 1. High-resolution computed tomography scan.](image-url)
Having compared gadolinium-enhanced MR cisternography and the conventional T2-weighted MR cisternography, the authors inferred that the former method is more effective in identifying the location of a CSF fistula [38, 40, 42]. However, taking into account the invasiveness of this procedure, it would be more reasonable to use it in the dubious or complex cases only.

Hence, the conventional MR cisternography and contrast-enhanced MR cisternography with endolumbar infusion of gadolinium are very accurate methods to identify location of a CSF fistula. They can be combined with other imaging techniques. However, since gadolinium-enhanced MR cisternography is expensive and invasive, these methods are recommended only when the results obtained using other tests are dubious [38, 40—42].

**CT cisternography.** To conduct CT cisternography, one needs to perform a lumbar puncture and perform a subdural infusion of the contrast agent. Next, a series of scans are recorded that can be used to verify CSF rhinorrhea and identify the location of a CSF fistula according to the extracranial distribution of the contrast agent, as it is done in MR cisternography (Fig. 3).

Seven studies devoted to CT cisternography reported that sensitivity of this method is 33—100%; specificity, 94%; and accuracy, 33—63% [43—49].

Single-photon emission CT cisternography was discussed in two studies as an alternative to the conventional CT cisternography for identifying the defect location. The sensitivity and accuracy of this method was 94 and 79%, respectively [47]; the overall sensitivity and accuracy of these methods used together was 94—100 and 91%, respectively [47, 48].

CT cisternography is less sensitive (33—72%) than MR cisternography (non-contrast-enhanced MR cisternography, 67—93%; MR cisternography with intrathecal gadolinium infusion, 80%) [44]. However, CT cisternography is less expensive than MR cisternography.

A number of authors reported [37, 50] that sensitivity of the two methods combined (MR cisternography and CT cisternography) increases to 100% and these diagnostic techniques are non-invasive.

Hence, although CT cisternography is less sensitive and accurate compared to other methods, it has been widely used to diagnose CSF rhinorrhea [37, 43—50].

**Fluorescein test.** Endolumbar injection of fluorescein allows one to accurately identify location of the skull base defect during either diagnostic endoscopy or surgical intervention (Fig. 4).

The fluorescein test has not been evaluated in literature yet, since there are no unambiguous recommendations regarding the dosage and the algorithm for administering this agent. The fluorescein diagnostic method was first used by F. Kirchner et al. back in 1960 [51].

Seven studies aimed at evaluating accuracy and safety of the fluorescein test were retrieved from the Pubmed database. It was reported in these studies that the defect was detected in 46—100% of cases [52—57]. According to R. Seth et al. [52], intraoperative administration of fluorescein has no statistically significant effect on the recurrence rate of CSF rhinorrhea.

An important question widely discussed in literature is whether this diagnostic tool is safe. As demonstrated by the recent studies, its adverse effects are directly dependent on dose and concentration of fluorescein; furthermore, they can be controlled. R. Keerl et al. [53] reported on their experience in diagnosing CSF rhinorrhea using the fluorescein test. In their case series, 420 fluorescein injections of 0.5—5% fluorescein at a dose of 0.5—2.0 ml (being equivalent to 2.5—100 mg) were made. J. Moseley et al. [54] surveyed 1,111 members of the American As-
sociation of Neurological Surgeons regarding the administration procedure of this agent. According to them, fluorescein is used at a dose of 0.1—5 ml of 5% fluorescein diluted in 0—10 ml of CSF. Serious adverse events were reported for the agent used at high doses (500—1250 mg): lower extremity paresis, generalized seizure activity, cranial nerve deficit, and death [55, 56]. When administered at a dose of 25—50 mg, fluorescein can cause minor adverse events that are related not only to fluorescein [55—57]. In the USA, fluorescein is typically used at the lowest possible doses and concentrations: 0.5—2.0 ml of 0.5% fluorescein (2.5—10 mg) diluted in CSF [58].

When performing the literature search, we have found 3 papers focused on the problem of topical application of fluorescein for diagnosing [58—60]. It was suggested that fluorescein should be applied topically into the nasal cavity. When mixed with CSF, the agent changes its color. The reported accuracy was 100%. However, no controlled studies using other clear fluids, such as nasal secretion or normal saline, have been conducted. Hence, it is unclear how high the percentage of false-positive reactions upon topical administration of fluorescein is.

The fluorescein test is one of the options to verify and identify location of a CSF fistula. The advantage of this method is that it is highly accurate and inexpensive, as well as performed in real time. However, new thorough studies are needed to elaborate the safest and most effective procedures for application of fluorescein [52—60].

Discussion

CSF rhinorrhea can be diagnosed using many methods. The present review demonstrates that the diagnostic tests vary greatly in terms of their sensitivity, specificity, accuracy, invasiveness, and cost. Although the data reported in the world literature are not sufficient for formulating accurate clinical guidelines, they have been used to develop an optimal algorithm to diagnose CSF rhinorrhea.

In 2002, J. Zapalac et al. [15] proposed an algorithm, which was modified by M. Gretchen et al. [35] in 2016. Diagnosing CSF rhinorrhea has two objectives: diagnosis verification and identification of defect location. Taking into account the accuracy and cost of the diagnostic tests, the authors have drawn a conclusion that beta-2 transferrin or beta-trace protein detection is the best method for verifying the diagnosis of CSF rhinorrhea, while HRCT is the optimal procedure for identifying the defect location.

After all the benefits and shortcomings of beta-2 transferrin test have been evaluated, this method still remains the best option for verifying the diagnosis of liquorrhea in the USA. The data reported in this review infer that beta-trace protein detection can be preferred, but this method is in unavailable in the USA.

Radionuclide cisternography is not recommended for routine practice because of its high cost, the existing risks, as well as low sensitivity, specificity and accuracy. Since no studies have recently focused on this method, it now can be considered in the historical context only.

According to M. Gretchen et al. [35], non-contrast-enhanced MR cisternography can be as effective for verifying the diagnosis of liquorrhea as radionuclide cisternography. Meanwhile, MR cisternography is non-invasive and more available. Hence, it is not possible to perform the beta-2 transferrin test or its results are dubious (e.g., because the amount of nasal secretion is insufficient), MR cisternography is the method of choice for verifying liquorrhea. These conclusions supplement the algorithm proposed by J. Zapalac et al. [15] who did not use this method back in 2002.

HRCT is still the method of choice for identifying the defect location as this procedure is easily accessible, non-invasive, and high-accuracy. Furthermore, it costs almost three times less than MR cisternography. Hence, we agree that HRCT is the first procedure to be performed to identify defect location as suggested in the algorithm by J. Zapalac and M. Gretchen et al. [15, 35].

All the recent studies dealing with CT [43—49] have been casting doubt on the supremacy of this method in identifying the fistula location because of its invasiveness, lower sensitivity, specificity, and accuracy compared to HRCT.

The fluorescein test can be used both for verifying the diagnosis of CSF rhinorrhea and to identify defect location (intraoperatively as well). However, the authors sug-
gest that it is used as a secondary method because of the significant risks related to fluorescein administration. In the study by J. Zapalac et al. [15], the fluorescein test ranked third, being inferior to HRCT and MR cisternography. However, many papers demonstrating that this method involving low-dose fluorescein administration is safe and highly effective have been published after 2002 [56—60]. Nevertheless, further research is needed on this topic to elaborate the optimal fluorescein administration procedures.

Table summarizes the data on sensitivity, specificity, accuracy, and cost of the methods. Overall, there have been few publications suggesting modification of the algorithm proposed by J. Zapalac [15] since 2002. An exception was that radionuclide cisternography was replaced with MR cisternography in the study by M. Gretchen et al. [35]. The updated algorithm is shown in Fig. 5.

The glucose test is currently used to verify the diagnosis of CSF rhinorrhea in Russia because there are no laboratories performing the beta-2 transferrin and beta-trace protein tests. In 2017, the M.M. Shemyakin—Ovchinnikov, the Federal Research and Clinical Center of Physicochemical Medicine, and the N.N. Burdenko National Scientific and Practical Center for Neurosurgery launched a collaboration project aimed at studying the level of beta-trace protein in nasal secretion. CT cisternography is still a routine method to detect liquorhrea and identify the defect location, since it is on the list of quota-based diagnostic methods. MR cisternography is not on the list of government-funded methods for diagnosing CSF rhinorrhea, so its use is limited. Fluorescein, the medicinal product synthesized at the Research Insti-

<table>
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<tr>
<th>Study method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost, USD</th>
<th>Invasiveness</th>
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<tbody>
<tr>
<td>Glucose test, %</td>
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<td>0—45%</td>
<td>Low</td>
<td>—</td>
</tr>
<tr>
<td>β2-transferrin test, %</td>
<td>87—100</td>
<td>71—100</td>
<td>37.90</td>
<td>—</td>
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<tr>
<td>β-trace protein test, %</td>
<td>91—100</td>
<td>86—100</td>
<td>20.31</td>
<td>—</td>
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<tr>
<td>High-resolution computed tomography</td>
<td>44—100</td>
<td>85—100</td>
<td>280.32</td>
<td>—</td>
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<tr>
<td>Computed cisternography, %</td>
<td>33—72</td>
<td>94</td>
<td>542.76</td>
<td>+</td>
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<tr>
<td>Magnetic resonance cisternography, %</td>
<td>56—94</td>
<td>57—100</td>
<td>807.34</td>
<td>—</td>
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<tr>
<td>Fluorescein test, %</td>
<td>73—100</td>
<td>100</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

Fig. 5. The algorithm proposed by Gretchen et al. in 2016.

CSF – cerebrospinal fluid; HRCT – high-resolution CT; MR cisternography – magnetic resonance cisternography.
tute of Organic Semiproduts and Dyes is an analogue of Fluorescein Novartis, the medicinal product manufactured abroad, that was approved in 2016. It is currently being actively implemented into clinical practice at the N.N. Burdenko National Scientific and Practical Center for Neurosurgery.

Conclusions

1. With allowance for sensitivity, specificity, accuracy, and cost of diagnostic tests, beta-2 transferrin and beta-trace protein detection tests are found to be the best techniques for verifying the diagnosis of CSF rhinorrhea; high-resolution CT is optimal for identifying the defect location.

REFERENCES


2. Unfortunately, the evidence included in this review is not sufficiently reliable for diagnosis of CSF rhinorrhea, which necessitates more accurate studies to be performed.

Author contributions

Study conception and design — E.V., N.A.
Data collection and processing — E.V., N.A.
Manuscript writing — E.V., N.A.
Manuscript editing — D.N., D.N., A.D.

Authors declare no conflict of interest.


Commentary

This paper reviews the modern methods used to diagnose CSF rhinorrhea according to the data reported in 47 publications. The problems related to diagnosing CSF rhinorrhea are presented and their relevance is clearly justified. The main techniques, along with their advantages and drawbacks, are thoroughly described in a clear and lucid manner.

The key statistical data (sensitivity, specificity, and accuracy) are reported, verifying the superiority of some diagnostic tests over the other ones. Special focus is also placed on safety analysis of the methods being used. The authors of the review offer an optimal diagnostic algorithm that will undoubtedly be of use for practitioners.

The authors draw one’s attention to the insufficient body of evidence and the absence of well-proven procedures (e.g., beta-trace protein and beta-transferrin detection in nasal discharge, fluorescein test) in Russia. Hence, those are objectives and goals for future research to be set to achieve higher quality of work.

This review is an example of modern study analyzing a vast body of literature. It will be extremely useful for the routine practice of neurosurgeons, otorhinolaryngologists, and other specialists encountering CSF rhinorrhea in their practice.

A. Kh. Bekyashev (Moscow, Russia)
The relationship between molecular genetic and metabolic disorders is one of the challenges of modern oncology. In this review, we consider lipid metabolism and its changes as one of the factors of oncogenesis of glial tumors. Also, we demonstrate that the genome and the metabolome are interconnected by a large number of links, and the metabolic pathways, during their reorganization, are able to drastically affect the genetic structure of the cell and, in particular, cause its tumor transformation. Our own observations and analysis of the literature data allow us to conclude that mass spectrometry is a highly accurate current method for assessing metabolic disorders at the cellular level. The use of mass spectrometry during surgery allows the neurosurgeon to obtain real-time data on the level of specific molecular markers in the resected tissue, thereby bringing intraoperative navigation techniques to the molecular level. The generation of molecular fingerprints for each tumor significantly complements the available neuroimaging, molecular genetic, and immunohistochemical data.

Keywords: neuro-oncology, lipids, oncogenesis, IDH1, IDH2, glioma, protein kinase C (PKC), mass spectrometry.

Abbreviations:
2-HG — (D)-2-hydroxyglutaric acid
DESI MS — desorption electrospray ionization mass spectrometry
ESI — electrospray ionization
IDH1, IDH2, IDH3 — isocitrate dehydrogenase 1, 2, 3
αKG — alpha-ketoglutaric acid
FA — fatty acids
MRI — magnetic resonance imaging
PKM — protein kinase M
PKC — protein kinase C
CNS — central nervous system

The problem of diagnosis and treatment of brain tumors is one of the most serious issues in modern oncology. According to the Central Brain Tumor Registry (USA), glial neoplasms account for about 31% of the total number of primary CNS tumors. Glioblastomas account for more than 50% of gliomas [1]. The incidence rates for diagnosed glium tumors depend on the histological type of the tumor, age of the patient at the time of diagnosis, gender, ethnicity and place of residence. According to the averaged data, incidence of all types of glial tumors is 4.67—5.13 cases per 100,000 population [2]. The incidence rates of glioblastoma diagnosis averaged by age are 0.89—3.69 cases per 100,000 population. Oligodendrogliomas and oligoastrocytomas have been shown to be more common among patients aged 35—44 years, while anaplastic astrocytoma and glioblastoma are more common in the age group from 75 to 84 years [1, 2]. In the latest version of the WHO CNS tumors classification (2016) [3], the emphasis in determining the type of tumor is made on the molecular biological features of neoplasms, since the properties of the genome and epigenome implemented by the cells are believed to be the key to novel methods of diagnosis and therapy of brain neoplasms [4—6]. To date, the standard for the treatment of glial brain tumors is the combined treatment: radical or supra-complete (resection of tissues beyond the boundaries of the contrasted part of the tumor) neurosurgical intervention using modern intraoperative navigation and
visualization systems in combination with subsequent chemotherapy and radiotherapy [1, 7—13]. During surgery, the surgeon faces serious challenges that require a quick response to a number of difficult questions. The most important of them are related to the definition of the morphological boundary “tumor—intact brain tissue”, rapid analysis of histological structure of the tumor, determination of the degree of its malignancy. Nowadays, traditional “slow” methods of histological examination of freshly frozen tissue samples are used to answer these questions, with sensitivity and specificity of these methods requiring improvement [14].

High demand for novel molecular approaches to differential diagnosis of brain tumors dictates the need for the development of integrated rapid methods that can provide reliable diagnosis of tumor characteristics. Such methods should accelerate the establishment of a definitive histological diagnosis and not be inferior to conventional histological examination in sensitivity and specificity.

One of the promising methods of highly accurate rapid diagnosis of tumors is tissue identification using mass spectrometry profiling methods. To date, the generally accepted approach involves methods of the so-called direct mass spectrometry, which combines the processes of microextraction of the studied molecules from a biological sample with their further ionization. The first studies describing tissue analysis using direct mass spectrometry were performed using desorption electrospray ionization (DESI), which utilizes interaction between charged droplets of water-methanol solution and the sample under study for microextraction of the target molecules from the sample with their subsequent ionization. This allows one to obtain data on the lipid profile of tumor tissue, as well as on the distribution of various water-soluble oncometabolites in the tissue [15—17]. The main lipid molecular markers used for identification of tissues by means of the abovementioned methods are saturated and unsaturated fatty acids (FA), glycerophosphoinositol, glycerophosphoserines, plasmemyn glycerophospho-ethanolamine lipids, and sulfatides. Mass spectrometry allows simultaneous profiling of the total lipid fraction, which includes both membrane structural lipids, free lipids (triglycerides), and etc. Despite the considerable number of papers [18, 19] devoted to the study of lipid profiles of brain tumor tissues, there is an acute need for integration of lipid profiling approaches in clinical, molecular genetic and immunohistochemical methods of diagnosis.

Lipid metabolism in glial tumors

G. Brante [20] revealed differences in lipid composition of intracranial tumors in comparison with healthy brain tissue in 1949. Later studies by K. Gopal et al. [21] showed that increase in the concentration of free FA, which is probably due to imbalanced lipid synthesis by the tumor, is representative of intracerebral tumor tissues. The results of recent studies have shown that higher FA, both free and within lipids, are the preferred energy substrate for glioma cells [22]. Human glioma cells primarily cultured in a serum-free mineral medium are able to oxidize free FA for respiratory and proliferative activity [23]. Studies on the use of glucose and acetic acid labeled with $^{13}$C carbon isotope administered both to cultured glioblastoma cells and patients immediately before surgery showed that gliomas demonstrate a pronounced shift in the preference of acetate glucose as an oxidizable substrate, as well as a significant decrease in the rate of glucose oxidation [24, 25].

Despite the fact that FA are the preferred energy substrate for glioma cells, it is possible that they are imported from the blood as well as synthesized in tumor cells. Once bound to mitochondrial membrane proteins, FAs are able to penetrate the plasma membrane, and this pathway can indeed serve as a source of nutrients in vivo. High availability of glucose in culture medium (under conditions of active transport of glucose into the cells) allows using it as a substrate for glycolysis, which leads to the synthesis of pyruvate, acetyl-CoA, and, finally, FAs. The resulting FAs can undergo aerobic oxidation by mitochondria in cells. The level of FA synthase expression in glioma cells was shown to significantly exceed the expression in healthy brain tissue and also elevate with an increase in glioma malignancy [26].

FA synthesis is a constant cellular process, with acetyl-CoA, which is derived via the Krebs cycle, serving as a substrate. Malonyl-CoA serves as the primer for the synthesis, it is formed via carboxylation of acetyl-CoA by acetyl-CoA carboxylase 1, which is then extended by FA synthetase yielding various long-chain FAs, such as palmitate [27]. Monounsaturated and polyunsaturated FAs are synthesized through activation of a set of FA-specific enzymes: stearoyl desaturase and FA desaturase 1 and 2. Metabolism of tumor cells is characterized by de novo synthesis of almost all FAs by these cells, with the enzymes serving as potential targets for tumor therapy [28, 29].

The set of synthesized FAs depends on the cell energy status and its current metabolic needs. For instance, FAs necessary for formation of membrane structures are synthesized during active proliferation, while FAs required for the synthesis of storage lipids are generated during proliferation delay [30]. It has been shown that FA synthesis is also maintained at low oxygen concentration in tumor tissue (which is explained by the lack of the need for oxygen during glycolysis), while, under conditions of low nutrient content, FA synthesis is activated by the signal cascade of hypoxia-inducible factor 1 alpha [31]. FAs are condensed into lipid droplets in the cytoplasm, which then serve as a depot for the energy and plastic metabolism of cells in hypoxia and in conditions of improving oxygenation [32]. It was found that peroxisome proteins, in particular peroxine 14, PMP70 and PPARα, increased
expression of which correlates with the degree of tumor malignancy, are actively involved in the accumulation of lipid droplets [33]. Inhibition of FA synthesis or beta-oxidation of FA reduces both the activity of glioma cell proliferation [23, 34] and the activity of normal neural stem cells [35, 36]. Such a double metabolic pathway provides energy and source for the growth of tumor cells and plays an extremely important role in carcinogenesis in malignant glial tumors.

FAs synthesized intracellularly or derived from the blood stream can be used for energy generation through mitochondrial and peroxisomal beta-oxidation while replenishing the substrates of the Krebs cycle. They also play an important role in anabolic processes within cells serving as a substrate for the synthesis of phospholipids that form part of plasma membranes and soluble glycerophospholipids acting as secondary messengers (components of signal cascades). FAs become a source of pre-cancerous signaling molecules (for example, endocannabinoids and eicosanoids) that activate the synthesis of various steroid hormones through the mevalonate pathway*, which is very active in glioblastoma cells [37]. FAs can act as a cofactor for the formation of lipid droplets under hypoxic conditions [32]. In addition, they can facilitate post-translational modifications (e.g., palmitoylation) of pro-oncogenic membrane proteins and protein complexes [38].

Thus, FAs play a diverse and important role in the functioning of tumor cells in gliomas. Almost all of the abovementioned lipid molecules associated with FAs serve as markers in the diagnosis of gliomas using the method of mass spectrometry and its modifications [18]. Nevertheless, the influence of a series of the most important genetic, molecular biological factors of carcinogenesis on the level and characteristics of lipid metabolism has not been studied well enough yet.

**Modern possibilities of mass spectrometry in neuro-oncology**

The pioneering work by L. Eberlin et al., published in 2010, [14] demonstrated that the use of DESI imaging allows obtaining characteristic lipid profiles (in particular, of structural sphingo- and glycerophospholipids) that allow molecular differentiation of astrocytic gliomas of different degrees of malignancy. The authors proposed an approach that can be used to identify gliomas by molecular profiling using DESI MS with further application of multivariate statistical analysis and machine learning. In this study, lipid profiles of 36 human gliomas, including oligodendroglioma, astrocytoma and oligoastrocytoma, were analyzed using DESI MS. Specific molecular patterns of intact gray and white matter have been determined in order to differentiate it from the glial tumor tissue, and classification criteria for rapid diagnosis were created on the basis of lipid spectra. G. Brante [20] noted differences in the lipid composition of intracranial tumor and normal brain tissues in 1949. Diagnostic indices in tumor samples revealed with the help of mass spectrometry coincided with expert diagnostic evaluation by pathologists for 79% of the signs tested [18].

Similar results were obtained by domestic researchers. A method that allows mass spectra of small samples (~1 mm³) to be obtained quickly (within a few seconds) has been developed [16]. The mass spectra analyzed by this method contain data on the lipid profile of the sample under study. Verification of the data was carried out by identification of lipids using their precise molecular weights, analysis of ion fragments of these lipids and distribution of the intensities of isotope peaks in the mass spectrum. It has been shown that a wide range of lipids can be identified in each sample using the developed approach, including lipids identified earlier by other laboratories. Based on the identified lipids, a database of lipid profiles corresponding to different types of brain tumors was generated. The database was compared with the available similar databases by other research groups specialized in the field of molecular profiling of brain tumors [14]. The level of data coincidence received by different groups is quite high. For instance, there were about 50% of matches between the database by Russian researchers and the database described in the study by L. Eberlin et al. [14]. The discrepancy in 50% of identifications can be explained by the difference in the methods of microextraction and ionization used by these groups, as well as by heterogeneity and biological variability of the samples. Nevertheless, the results of the studies are reproducible, which makes it possible to use the method to create tissue classifiers according to the mass spectrum of a mixture of substances extracted from a tissue [15, 16].

E. Zhvansky et al. [15] examined glioblastoma biopsy samples using this method and demonstrated that the method of lipid profiling can be used as the basis for the approach to the analysis of the composition of a heterogeneous tumor tissue sample, including cells of intact or necrotic tissues. As a result of this analysis, classification criteria were developed to determine the presence of various types of tissues (primarily intact brain and tumor tissues) in the sample. Preliminary results indicating differences in the mass spectra profiles of various histological types of tumors were also obtained using the proposed classification methods. Thus, development of specific algorithms for the analysis of spectra is required for the practical application of direct mass spectrometry methods and direct extraction of lipids from tissues. The same group of authors [17] proposed an algorithm developed for the analysis of direct mass spectrometry data for identification of morphological boundaries of a tumor tissue.

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*The mevalonate pathway is one of the most important metabolic pathways in eukaryotic cells, it leads to formation of two precursors of the terpenoid class, namely isopentyl pyrophosphate and dimethylallyl pyrophosphate, from acetyl-CoA molecules. These compounds further participate in the formation of various biomolecules: cholesterol, heme, vitamin K, and steroid hormones.

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The results obtained by the authors are in good agreement with the results of L. Eberlin et al. [19], who demonstrated high reliability of a classifier developed using lipid profiles for oligodendrogliomas, astrocytomas and meningiomas of different histological types and degrees of malignancy. The diagnosis based on the mass spectrometry data on the molecular profile of the tumor was consistent with the results of conventional histological analysis (microscopy of the sections following staining with hematoxylin and eosin) for all samples. Assessment of differences between different histological types of tumors, as well as differences depending on the degree of malignancy within one type of neoplasm was made. The results of mass spectrometry profiling of tumors were compared with preoperative MRI data using intraoperative neuronavigation.

The question on the relationship between the above-mentioned metabolic parameters determined using mass spectrometry and the most important molecular biological features of tumor cells remains to be interesting and relevant to date. The most important factors are mutations in the IDH1 gene and activity of atypical isozymes of protein kinase C (PKC), since they (IDH1 mutation as the primary genetic link, and atypical PKC as the main pleiotropic effectors) are involved in all aspects of the vital activity of tumor cells (catabolic, anabolic, genetic and epigenetic processes) while being the most important modulators of carcinogenesis.

Role of IDH mutations in carcinogenesis and their relationship with lipid metabolism

Enzymes of the isocitrate dehydrogenase family are represented by three isozymes located both in the cytoplasm (IDH1) and intracellular compartments, namely peroxisomes and mitochondria (IDH2, IDH3) [39]. All of them participate in oxidative phosphorylation processes: conversion of isocitrate to alpha-ketoglutarate (direct and reverse reactions), with IDH3 catalyzing this process within the cycle of tricarboxylic acids only in the forward direction yielding 2-oxoglutarate [40, 41].

Works on the mapping of isocitrate dehydrogenase genes were started as far back as in the 1970s. In 1985, K. Narahara et al. [42] found that IDH1 gene is located on the short arm of chromosome 2 (2q33.3). In 1996, T. Huh et al. [43] showed that IDH2 gene is located on the short arm of chromosome 15 (15q26.1). Interestingly, IDH3 is a heterotrimeric complex and encoded by several genes: IDH3A, which is located on the short arm of chromosome 15 (15q26.1); IDH3B localizing on the long arm of chromosome 20 (20p13), and IDH3G located on the short arm of the X chromosome (Xq28) [41, 43—46].

Mutations in the IDH genes include somatic, heterozygous, and point mutations in the active centers of the enzymes, with IDH1 mutations featuring arginine replacement being located in the 132nd-codon (arg132), while the same mutations for IDH2 are located in the 140th or 172nd-codons (arg140, arg172) [39, 47]. It is peculiar that these mutations are found only in the heterozygous state and associated with an increase in the enzyme activity. Thus, mutant forms IDH1 and IDH2 lead to the formation of D-2-deoxyglutarate from the alpha-ketoglutarate, the excess of which, in its turn, leads to suppression of alpha-ketoglutarate-dependent dioxygenases involved in DNA repair and histone demethylation [48]. All of this leads to hypermethylation of histones and DNA (especially in the CpG-rich regions) in mutant cells, which, in turn, triggers epigenetic changes with tumor cell transformation [49—51]. Some authors [41] believe that mono- or biallelic mutations in the IDH3 gene do not activate carcinogenesis but rather lead to suppression of ATP production in the mitochondria and result in cell apoptosis by inhibiting the tricarboxylic acid cycle.

IDH mutations in glioma cells

According to D. Krell et al. [52], IDH1 mutation is present in about 70% of Grade II—III gliomas and primary glioblastomas and only in 5% of secondary glioblastomas. IDH2 mutation is less common among Grade II—III gliomas. It has been recently shown that IDH1 and IDH2 gene mutations are prognostic factors of delayed tumor progression and increase in overall survival of patients [53—55]. To date, the mutational status of IDH1 and IDH2 is one of the main prognostic and diagnostic characteristics of astrocytomas that is widely used in the new classification of the nervous system tumors by WHO [56]. These features of mutated tumors have not been sufficiently studied. It has been shown that the IDH1 or IDH2 allele mutation leads to the large-scale changes in various components of carcinogenesis. For instance, hyperproduction of 2-hydroxyglutarate occurs in cells carrying this mutation, which leads to significant rearrangements in the epigenetic regulation of genome activity: the study of the epigenome of a large set of “intermediate” gliomas demonstrated significant hypermethylation of a number of genome regions. Introduction of the mutant allele of the IDH1 gene into cultured human astrocytes alters the patterns of specific methylation and acetylation of histones, induces extensive DNA hypermethylation, and rearranges methylome of the cells making it similar to the methylome of gliomas with a lower degree of malignancy [57]. In addition, the epigenetic changes resulting from IDH1 mutation lead to inactivation of a series of proto-oncogenes. At the same time, epigenetic stimulation of a number of mechanisms that promote some destabilization of the cell’s genome is also observed [58].

An important role is played by genetic changes that arise due to the mutation of IDH1 and IDH2 genes. A series of studies [59] revealed both activating and inactivating effects of IDH mutation on various proto-oncogenes such as PIK3CA, KRAS, AKT, N-MYC, and etc. [59]. The role of IDH genes in activation of angiogenesis,
which plays an essential role in tumor progression and invasion, has been demonstrated [60].

Interesting data have recently been obtained on the relationship of IDH1 and IDH2 mutations with changes in the DNA repair processes in tumor cells. An increased production of 2-hydroxyglutarate (2HG) induced by IDH mutations was found to result in a significant decrease in the activity of homologous recombination processes, which is one of the key factors in restoration of the native genome structure and an important component of cellular anti-oncogenic mechanisms. Thus, IDH1 and IDH2 mutations lead to a decrease in the activity of anti-oncogenic mechanisms and increase in genome instability [61, 62].

New data revealing the presence and nature of the relationship between 2HG and lipid metabolism in tumor cells have been published. In a recent study [30], an unusual pathway for lipid synthesis was discovered, in which glucose carbon is used for generation of alpha-ketoglutaric acid (αK⁄G) in mitochondria, which is then transported to the cytosol where it serves as a substrate for reductive carboxylation by isocitrate dehydrogenase 1 (IDH1). The resulting citrate is then cleaved with the synthesis of lipogenic acetyl-CoA thereby completing a new pathway of glucose-dependent reductive carboxylation. Cells with dysfunctional IDH1 exhibit impaired synthesis of lipids from glucose or glutamine, which suggests the requirement for the wild-type IDH1 allele as the most important component of the synthesis of fatty acids in tumor cells [63]. This study demonstrates the direct relationship between the IDH1 mutation and lipid metabolism, while the effect of this mutation on the lipid spectra of tumors of various degrees of malignancy remains poorly understood.

Role of atypical isoforms of protein kinase C in carcinogenesis and lipid metabolism

Protein kinases C are key elements of a series of proliferative cascades. Members of this family include such protein kinases as PC ζ, PC Mζ and PC C. These enzymes have unusual properties, in particular, their catalytic activity is higher than for other members of this class. It should also be noted that the PC Mζ has the property of maintaining its own activity, since, unlike other representatives of this class, it does not have autoinhibitory domains but, instead, contains autocatalytic domains [64].

Several members of this class of proteins participate in the development of tumor diseases of various localization. Their direct role in carcinogenesis is associated with the involvement of atypical PKC isoforms in the processes of cell proliferation and growth, as well as in changes in the cytoskeleton properties in a series of tumor cells and their adhesiveness properties [65, 66].

The role of protein kinase Cζ in oncology

A number of studies have shown the role of PKCζ in regulation of the growth of primary tumor cells and implementementation of the mechanisms of metastasis in breast, colon, and hepatocellular carcinoma [67—69].

The role of PKCζ in brain tumors is much less studied as compared to other localizations of the tumor process. Thus, one of the studies demonstrated that PKCζ participates in modulation of glioblastoma cell migration and invasion by regulating cytoskeleton rearrangements, changing cell adhesiveness and stimulating increased expression of matrix metalloproteinase-9 [70]. It was also found that the activity of PKCζ in glioblastoma cells is largely related to the tumor necrosis factor (TNF) system and plays an important role in carcinogenesis [71].

Protein kinase Mζ in development of oncological diseases

The role of protein kinase Mζ (PKMζ) in the development of tumor diseases has not been studied as well and in detail as the role of its “elder sister”, PKCζ, due to the fact that this form has been found only recently. One of the few studies revealed the involvement of this form of protein kinase in the development of acute lymphoblastic leukemia [72]. There were no studies on the role of PKMζ in the development of glial brain tumors. Nevertheless, it was found that PKMζ is involved in proliferation of neurons during neurogenesis and may be also involved in proliferative cascades in the cells of astrocytic glia [73]. These studies show the prospect of considering the role of these protein kinases in the development of brain tumors.

The role of protein kinase C in the pathogenesis of brain tumors

High activity of protein kinase C (PKC) is known to be observed in malignant tumors of lung, gastrointestinal tract, ovaries and breast [74—78].

Several studies [79] demonstrated the involvement of PKC in the development of glioblastoma. These observations indicate that the enzyme can be a successful target for therapeutic inhibitors [80, 81]. At the same time, there were no studies on identification of the involvement of PKC in the pathogenesis of various types of glial tumors, as well as glial tumors of various degree of malignancy.

Role of atypical isoforms of PKC in carcinogenesis in the aspect of lipid metabolism

According to numerous studies, one of the key proto-oncogenic factors synthesized from lipids is the secondary messenger diacylglycerol, the presence of which in the medium leads to activation of mitogen-activated protein kinases (MAPK cascade), which play an important role in cell division processes. PKCζ is one of the most important effectors of the MAPK cascade, it determines the main effect of the cascade on the proliferative activity of the cell. It is the activation itself that ensures functioning of the mitogenic pathway triggered through the platelet-derived growth factor receptors, which, in turn, is one of the key triggers of tumor growth in gliomas [82].
Moreover, it has been shown that PKCζ, PKCI and PKCA are the most crucial factors regulating the synthesis of a number of FAs and lipid derivatives that serve as indicator metabolites of tumor cell transformation in mass spectrometry studies [83, 84]. Various PKC iso-enzymes can be differentially activated by lipids, which plays an important role in carcinogenesis [85]. Thus, atypical isoforms of PKC are the key components of the cell lipid metabolism pathway, which determine both lipids synthesis and their functions involved in the process of carcinogenesis.

Conclusion

Modern technical solutions based on the best practices of physical and chemical sciences are increasingly involved in medical practice. Mass spectrometry, which has been an important tool in the hands of fundamental medicine and biology over the past decades, is now close to become a part of surgical practice. There is no doubt that this approach is justified and necessary: mass spectrometry opens up new interesting perspectives in rapid integrated diagnosis of various diseases, including intraoperative diagnosis. The problem of reliable and at the same time sufficiently rapid methods of diagnostic search within the framework of the surgical process remains very relevant nowadays. The value of mass spectrometry for analysis of the biological material for surgery can be very high, it allows establishing the most important diagnostic parameters, similar to those determined using conventional histological study quite fast and with sufficient accuracy.

Nevertheless, the parameters of lipid metabolism that are indicative for mass spectrometry are only a metabolic result of the fundamental molecular biological processes underlying tumor development. Therefore, the most important problem is the establishment of the relationship between the key molecular biological parameters of the tumor with the characteristics of lipid metabolism determined by mass spectrometry analysis of the neoplasm.

Analysis of the literature showed that mutations in IDH1 and IDH2 genes are one of the most important genetic factors affecting the processes of carcinogenesis in gliomas. The key role of these mutations in establishing the prognosis and biological characteristics of glial tumors is due to the presence of pleiotropic effects on most key intracellular links of tumor progression. The presence of mutations in IDH1 and IDH2 genes changes the activity of proto-oncogenes, DNA hypermethylation status, modifies DNA repair system, and also has a global impact on the epigenetic regulation of the genome functioning. At the same time, the product of the mutant gene has a direct effect on the synthesis of a number of lipids. Thus, mutations in IDH1 and IDH2 significantly alter the parameters of lipid metabolism both indirectly, by modifying global intracellular processes, and directly, by affecting the synthesis of lipid metabolites.

It is quite possible that the atypical isoforms of PKC are the main executive link in the processes responsible for mutations of not only IDH1 and IDH2 isoforms but also other genetic and epigenetic modifications of the genome in tumor cells. Proteins of this class fully correspond to the pleiotropic action of the above-described mutations of IDH1 and IDH2 in their functional capabilities and action: their influence on intracellular metabolism and functional status of global regulatory systems is also diverse. Functional versatility of these enzymes include their key role in proliferative cascades, regulation of proto-oncogene activity, cell adhesiveness and various processes of metabolism and many other functions as well. In general, the effect of atypical isoforms of PKC on the characteristics of lipid metabolism also looks dual: there is a combination of direct and indirect interference with the activity of these proteins in lipid metabolism.

Thus, mutations in IDH1 and IDH2 genes and expression of atypical isoforms of PKC have both a direct and indirect effect on the main characteristics of lipid metabolism. Mass-spectrometry methods can be successfully used for indirect rapid diagnosis of these mutations.

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