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4-ya Tverskaya-Yamskaya ul., 16,
Moscow, 125047
Russia
Burdenko Neurosurgical Institute
Tel. +7 (499) 972 8566
E-mail: Vopr@nsi.ru
Managing Editor
V.K. Ivannikova
E-mail: Vlivanikova@nsi.ru

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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.

**Topics to be covered in our next issue:**

- Neuroimaging and navigation in treatment of spinal tumors
- Intraoperative Doppler ultrasound in endoscopic transsphenoidal surgery
- Clinical recommendations for traumatic brain injury (Part 3)
Diffusion Tensor Imaging Tractography and Intraoperative Neurophysiological Monitoring in Surgery of Intracranial Tumors Located Near the Pyramidal Tract

V.YU. ZHUKOV1, S.A. GORYAYNOV1, A.A. OGURTSOVA1, I.S. AGEEV2, S.V. PROTSKIY3, I.N. PRONIN1, A.S. TONOYAN1, G.L. KOBYAKOV1, E.A. NENASHEV4, A.S. SMIRNOV1, A.I. BATALOV3, A.A. POTAPOV1

1Burdenko Neurosurgical Institute, Moscow, Russia; 2Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia; 3Nizhnegorsk Central District Hospital, Crimea, Russia; 4Volynskaya Hospital, Moscow, Russia

Background. Implementation of methods for intravital examination of the brain pathways, such as preoperative diffusion tensor imaging (DTI) tractography and intraoperative neurophysiological monitoring, enables safer resection of intracranial tumors located near the pyramidal tracts (PTs). Purpose. The purpose of this study was to investigate the relationships between intracerebral tumors of different histological types and the pyramidal tract using preoperative DTI tractography and various methods of intraoperative neurophysiological monitoring for intraoperative identification of the pyramidal tract, including different variants of the topographo-anatomic relationships between the pyramidal fascicle and the tumor. Material and methods. The study included 29 patients with supratentorial tumors of different histological types. Of these, 2 patients had grade I tumors, 8 patients had grade II tumors, 4 patients had grade III tumors, 11 patients grade IV tumors, and 4 patients had brain metastases. The patients underwent preoperative DTI tractography with PT reconstruction and evaluation of the topographo-anatomic relationships between the pyramidal tract and the tumor (tract: intact, infiltrated, displaced). Neurophysiological monitoring (direct electrical stimulation in 24 patients and transcranial motor evoked potentials in 26 patients) was used during the surgery. The strength of stimulating current for direct stimulation ranged from 10 to 30 mA. Postoperatively, the motor function was evaluated using a 5-score scale, and the data were compared to the preoperative data. Results. According to preoperative DTI tractography in patients with grade I—II gliomas, the corticospinal tracts were infiltrated in 2 cases, displaced in 3 cases, and intact in 5 cases. In patients with grade III—IV gliomas and metastases, the tracts were infiltrated in 8 cases, displaced in 4 cases, and intact in 7 cases. Motor responses evoked by direct electrical stimulation were obtained in 5 out of 6 patients with the pyramidal tract displaced by the tumor and in 7 out of 8 patients with the tract infiltrated by the tumor. In the case of the intact tract, the PT to tumor distance and the stimulus strength play an important role; the responses were obtained in 4 out of 10 patients. In case of transcranial motor evoked potentials (TCMEPs), no dynamics of the potential amplitude was detected in 17 out of 26 patients during surgery; reduced TCMEP amplitude was observed in 9 patients. Conclusions. 1. Patients with an infiltrated or displaced pyramidal tract significantly more often had hemiparesis before surgery and aggravation of hemiparesis after the surgery compared to patients with an intact tract. 2. In the case of direct electrical stimulation of the PT, motor responses were significantly more often observed for the pyramidal tract infiltrated and displaced by the tumor (according to preoperative DTI tractography). 3. A reduction in the motor neurologic deficit in the postoperative period was significantly more often observed for application of stronger current during direct electrical stimulation. 4. Consistency of the TCMEP amplitude during the surgery is a reliable predictor for no aggravation of the motor neurologic deficit after the surgery. Postoperative aggravation of hemiparesis was significantly more often observed when TCMEPs decreased during the surgery.

Keywords: glioma, metastasis, DTI tractography, intraoperative neurophysiological monitoring, direct electrical stimulation, transcranial motor evoked potentials.

Abbreviations

DTI tractography — diffusion tensor imaging tractography;
TCMEP — transcranial motor evoked potentials;
PT — pyramidal tract;
ES — electrical stimulation

The current incidence of primary brain tumors is 11—12 cases per 100 000 of population; glial tumors account for 40—55 to 80% of all central nervous system tumors and consist of 40% of anaplastic astrocytomas and of 50% of glioblastomas [1—3]. Combined treatment strategy, which includes surgery and subsequent chemoradiotherapy, is the accepted standard of care in most cases [4, 5]. The best possible surgical removal of the tumor is an extremely important factor that affects the efficacy of all subsequent treatment stages. J. Nazzaro and E. Neuwelt [6] define the goal of surgery in treatment of supratentorial gliomas as following: reduction of mass effect and intracranial hypertension; reduction of tumor volume; proper histological diagnosis. Due to the infiltrative growth pattern it is very challenging to identify edges of glial tumors and their topographo-anatomic relationships with the adjacent brain structures, particularly PT, intraoperatively.

Information on topographo-anatomic location of the tumor relative to the PT is extremely important in surgery of brain gliomas located near the pyramidal tract. These data can be obtained both preoperatively (using DTI tractography) and intraoperatively (using direct ES) [7].

The interest in intravital examination of the brain pathways has increased in the last decade with advent of DTI tractography. It became possible to plan surgery and resection of the tumor...
mass, taking into account the relationship between the topographic-anatomic pathways and location of the pathology [8]. DTI tractography allows visualization of the main conductive paths of the brain based on their actual anatomical localization [9—12]. Direct subcortical ES is used for identification of the PT during the surgery [13—15]. Transcranial motor evoked potentials (TCMEP) are used intraoperatively to monitor PT function [16, 17]. Below, we present the data on the joint use of DTI tractography and neurophysiological control methods (direct ES, TCMEP) in surgery of intracerebral tumors (Table 1).

As can be seen from Table 1, combined use of preoperative (DTI tractography) and intraoperative neurophysiological monitoring methods has an additive effect in the surgery of intracranial brain tumors [18].

The purpose of this study was to investigate the relationships between intracerebral tumors of different histological types and the pyramidal tract using preoperative DTI tractography and various methods of intraoperative neurophysiological monitoring for intraoperative identification of the pyramidal tract, including different variants of the topographic-anatomic relationships between the pyramidal fascicle and the tumor.

Material and Methods

The study included 29 patients (13 men and 16 women; average age of 45 years) with tumors of different histological types. Of them, 2 patients had grade I tumors, 8 patients had grade II tumors, 4 patients had grade III tumors, 11 patients grade IV tumors, and 4 patients had brain metastases (Figure 1).

All tumors were supratentorial. The patients underwent preoperative DTI tractography with PT reconstruction and evaluation of the topographic-anatomic relationships between the pyramidal tract and the tumor (tract: intact, infiltrated, displaced). Direct ES was performed in 24 of 29 patients, MEPs were registered in the muscles in the contralateral limbs and half of the face. Bipolar two-contact electrode was used and the stimulation was also conducted by sequences, consisting of 4 rectangular pulses with a duration of 0.5 ms and a frequency of 500 Hz. In one unit the sequences were initiated only once after a button was pressed, while in the other they were delivered rhythmically with a frequency of 1.0—1.2 Hz.

Transcranial motor potentials were evoked in 26 out of 29 patients. The stimulating electrodes were collated subcutaneously on the scalp at C3—C4 points. The recording needle electrodes are located on the muscles of the upper (m.biceps/triceps brahii, m.tenar) and lower (m.rectus femoris/ biceps femoris, m.gastrocnemius) limbs. The stimulation was carried out in batches, sequences, consisting of 4 rectangular pulses with a duration of 0.5 ms and a frequency of 500 Hz. We evaluated the amplitude of the MEP (its dynamics), and the degree of MEP stability and changes in the level of motor stimulation threshold.

Postoperatively, the motor function was evaluated using a 5-score scale, and the data were compared to the preoperative data. DTI tractography and MRI were performed on MRI machine with magnetic flux density of 3.0 T using an echoplanar spin echo pulse sequence (SE-EPI), three values of the diffusion factor b (0, 1000 and 2500 s/mm²) and 60 directions of diffusion gradients for each non-zero b-factor. The following parameters for set to the following values: time, TR=10,000 ms, TE=103.4 ms, FOV=240×240 mm, image matrix of 80×80 with subsequent interpolation up to 256×256, slice thickness of 3 mm, distance between the slices of 0 mm, NEX=1, axial scanning plane.

Statistical analysis was performed in Statistica 10.0 software package: descriptive statistics and methods of rank correlation for nonparametric parameters, including dichotomous ones, such as Spearman, Kendall Tau, and Gamma coefficients, were calculated.

Results

Preoperative DTI tractography

Three types of relationships have been putatively identified between the tumor and the pyramidal tract: intact, displaced, and infiltrated. Intact tract is located far away from the tumor and its perifocal edema zone, the fascicle pathway and its thickness are unchanged. The infiltrated fascicle is located in the tumor area, partly overlaps with it and is thinned. The displaced tract runs along the edge of the tumor, changing its trajectory. Below are the details of the relationships between the group of tumors in the study and the pyramidal fascicle based on DTI tractography data (Table 2).

As can be seen from Table 2, the PT was intact in 7 (36.8%) out of 19 patients with grade III—V gliomas and metastases and in 5 (50%) out of 10 patients with grade I—II gliomas. Tract infiltration was observed in 8 (42.1%) out of 19 patients with grade III—IV gliomas and metastases and in 2 (20%) out of 10 patients with grade I—II gliomas. The PT was displaced in 6 (31.6%) out of 19 patients in the subgroup with malignant gliomas and metastases and in 3 (30%) out of 10 patients in the subgroup with benign gliomas.

Neurological status in the pre- and post-operative period and the PT status based on DTI tractography data

According to our data, the patients with the PT displacement and infiltration significantly more frequently had neurological deficits prior to the surgery (Spearman rank correlation: r=−0.478; p=0.00864) (Fig. 2) and more frequently experienced neurological deficit after the surgery, e.g. more frequently displayed negative neurological dynamics (Gamma rank correlation: r=0.41; p=0.027) (Fig. 3).

The pre-operative photographs display relationships of the PT and the tumor (Fig. 4).

The examples of topographical relationships between the tumor and the pyramidal tract (Fig. 4).

Therefore, malignant intracranial tumors and metastases are associated with higher frequency of the PT infiltration and displacement.

Intraoperative neurophysiological monitoring: direct electrical subcortical stimulation

Direct stimulation of the subcortical sections was performed in 24 patients. After the direct stimulation, motor responses were evaluated in the face and the contralateral limbs. Motor responses were observed in 5 out of 6 patients with the tumor-displaced PT and in 7 out of 8 patients with tumor infiltration into the tract. In case of the intact tract, the distance from the tumor and the strength of the stimulus were important factors and the responses were obtained in 4 out of 10 patients (Table 3).

The comparison of the results of direct ES and the status of the pyramidal tracts based on pre-operative MRI data (intact,
displaced, infiltrated fascicle) revealed a statistically significant correlation between the tumor proximity (infiltration and displacement) to the PT and the frequency of motor responses (Spearman rank correlation: \( r=0.45; p=0.0273 \) (Fig. 5 and 6).

The use of higher intensity of intraoperative direct current was associated with significantly less frequent increase in motor neurological deficit in the post-operative period. Conversely, lower current intensity over the course of direct ES was associated with significantly more frequent increase in motor disorders in the post-operative period (Gamma rank correlation: \( r=-0.457; p=0.018 \), Figure 7).

Intraoperative neurophysiological monitoring: transcranial motor evoked potentials

TCMEP monitoring was performed in 26 patients with intracerebral tumors. As can be seen from Table 4, the amplitude of the potential remained unchanged over the course of the surgery in 17 patients (including 2 patients with aggravation of hemiparesis). The amplitude of TCMEP decreased in 9 patients (including 7 with aggravation of hemiparesis and 2 with no change).

TCMEP were stable in 17 out of 26 patients; no aggravation of hemiparesis was observed in 15 out of 17 patients in the postoperative period. The decrease in TCMEP was observed in 9 patients, and postoperative aggravation of hemiparesis was observed in 7 patients. The preoperative DTI tractography revealed that most patients with a decrease in TCMEP had infiltrated PT. Therefore, there was a statistically significant correlation between the preservation of TCMEP during the surgery and no increase in neurological deficit after it (Spearman rank correlation: \( r=-0.704; p=0.00002 \) (Fig. 8).

**Clinical cases**

**Clinical case No 1**

Patient K., 46 years old, male. Diagnosis: glioblastoma of the left insular lobe. According to the patient, he was apparently healthy when on September 05, 2014 he experienced an attack of numbness in the right extremities, which resolved within a few minutes. MRI revealed a tumor in the left insular lobe, which intensively accumulated contrast agent (Fig. 9a, b, c). There were no signs of intracranial hypertension. No hemiparesis was identified before the surgery. Primarily

![Figure 1. Distribution of patients by nosology.](image)

1 — Grade I; 2 — Grade II; 3 — Grade III; 4 — Grade IV; 5 — metastases.

**Table 1. The role of DTI tractography and subcortical stimulation in brain tumors surgery**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Methods</th>
<th>Type of pathology</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Berman, M. Berger, S. Chung, S. Nagarajan, R. Henry, 2007 [8]</td>
<td>9</td>
<td>DTI tractography Subcortical stimulation</td>
<td>Gliomas</td>
<td>DTI tractography can be used to determine direction of the pathways in the depth of the white matter</td>
</tr>
<tr>
<td>L. Bello, A. Gambini, A. Castellano, et al., 2008 [30]</td>
<td>64</td>
<td>DTI tractography Subcortical stimulation</td>
<td>Gliomas</td>
<td>Combination of DTI tractography and subcortical stimulation allows accurate identification of eloquent fiber tracts and enhances surgical performance and safety while maintaining a high rate of functional preservation</td>
</tr>
<tr>
<td>K. Kamada, T. Todo, T. Ota, et al., 2009 [29]</td>
<td>40</td>
<td>DTI tractography TCMEP Direct ES</td>
<td>Gliomas, ABM, DNET, PNET, metastasis</td>
<td>The investigators found that DTI tractography is a reliable way to map the white matter connections in the entire brain. By combining these techniques, one can investigate the cortical-subcortical connections in the human CNS.</td>
</tr>
<tr>
<td>S. Ohue, S. Kohno, A. Inoue, et al., 2012 [23]</td>
<td>32</td>
<td>TCMEP Preoperative and postoperative DTI tractography</td>
<td>Gliomas</td>
<td>DTI tractography is a reliable and accurate method for mapping the course of subcortical sections of the tract. Intraoperative neurophysiological methods are useful for minimizing neurological deficit after the surgery.</td>
</tr>
<tr>
<td>S. Ostrý, T. Belšan, J. Othál, et al., 2013 [46]</td>
<td>25</td>
<td>Preoperative DTI tractography Direct intraoperative ES DT Tractography</td>
<td>Gliomas, methastases</td>
<td>The combination of these two methods in some cases can help to increase the safety of tumor resection near the PT.</td>
</tr>
<tr>
<td>F. Vassal, F. Schneider, C. Nuti, 2013 [47]</td>
<td>10</td>
<td>DTI tractography Direct ES</td>
<td>Gliomas</td>
<td>The use of anatomical (DTI tractography) and functional (subcortical stimulation) techniques allows more accurate resection of a tumor near the eloquent motor areas</td>
</tr>
<tr>
<td>M. Ottenhausen, S. Krieg, B. Meyer, F. Ringel, 2015 [18]</td>
<td>Review</td>
<td>DTI tractography Direct stimulation of the cortex Subcortical stimulation</td>
<td>Gliomas</td>
<td>Combination of neuroimaging and neurophysiological monitoring techniques allows more accurate and safer resection of the tumor near the eloquent cortical regions</td>
</tr>
</tbody>
</table>
paroxysmal symptoms manifested as focal epileptic seizures accompanied by the right-sided hypesthesia. Marked PT infiltration with the tumor based on the data of the preoperative DTI tractography (Fig. 9d, e).

TCMEP and direct subcortical ES were performed during the surgery. TCMEP at subcortical stimulation decreased during the process of the tumor resection, motor responses were obtained in the tumor bed (20 mA). Mild right hemiparesis and sings of aphasia of sensorimotor elements were observed on Day 1 after the surgery. Positive neurological dynamics on Day 3 after the surgery: regress of sensorimotor aphasia and increase in strength of the right extremities up to 4 points.

In this case, the clinical example demonstrates the infiltration of tumor into the PT (according to the preoperative DTI tractography). During the surgery, there was a decrease in TCMEP, direct ES resulted in motor responses in the bed of the resected tumor. After the surgery, there was an aggravation of hemiparesis.

**Clinical Case No 2**

Patient B., 33 years old, female. Diagnosis: diffuse astrocytoma of the left insular lobe. In mid-May 2014 she developed weakness in her right leg, and then in her right arm, which resolved after 3 days.

MRI detected a tumor in the left insular lobe (Fig. 10a, b). The tumor of the left insular lobe was removed surgically using neurophysiological monitoring. During the surgery, motor responses were obtained for direct subcortical ES (20 mA). TCMEP amplitude decreased during the surgery. Preoperative DTI tractography revealed that the left PT is thinner than on the healthy side and is infiltrated by the tumor (Fig. 10c). Postoperative DTI tractography (Fig. 10d) shows that a portion of the PT fibers (yellow color) is absent compared to the intact tract (blue color). This could be due to direct damage to the PT during the surgery, and therefore may be associated with the postoperative aggravation of hemiparesis up to 3 points. By the time of discharge, the severity of hemiparesis has decreased.

**Discussion**

Despite the application of our knowledge of somatotopical organization of the cortex and pathways [19], the outcomes of surgical resection of intracerebral tumors located near the pyramidal tract are rather unsatisfactory. For example, for this category of patients the rate of postoperative aggravation of hemiparesis amounts to 27% in the early postoperative period and in 13% of patients it does not resolve even in the long term [15]. Planning of surgical interventions based on assessment of topographic-anatomic relationships between the PTs and the tumor is crucial for improving the quality of surgical treatment. There are three types of spatial relationships: infiltrated, displaced, and intact tract [20].

Infiltration of the tract by the tumor is significantly more common in malignant processes, and therefore these patients have worse neurological outcomes of the surgery [21, 22]. The use of preoperative DTI tractography data and their integration into the neuronavigation system allows visualization of a distance from the tract to the tool during the tumor resection. However, inaccuracies can occur due to displacement of brain structures [7, 23]. Therefore, direct ES remains the method of choice for evaluating PT localization in during the resection of intracerebral tumors. At the same time, the use of DTI tractography, in our opinion, allows the surgeon to more carefully plan the operation and offers obvious benefits.

Thanks to modern MRI technologies, neurosurgeons have access to information on functionally important areas of the cortex, paths and metabolism in patients with brain gliomas [24—27]. DTI tractography, which allows visualization of the main conductive paths of the brain in based on their actual anatomical location, is one of the most widely used methods [12, 28]. This technique became widely used in clinical practice due to its accessibility and information content and its ability to convey information about relationships between intracerebral tumors and brain conductive pathways. The accuracy of DTI tractography in surgery of intracerebral tumors has been demonstrated in several studies [8, 29, 30].

Unfortunately, DTI tractography has a number of limitations. For example, most of the PT cannot be visualized in case of large peritumorous edema due to reduction in fractional anisotropy in the edema area, even though the PT is located in this place and be found by stimulation [22]. The strength of the stimulus and the distance to the path play very important role in subcortical direct stimulation which is performed to identify the pathways [30]. How careful and meticulous a neurosurgeon is in conducting electrical stimulation to find the pathways is also important.

DTI tractography cannot identify the cortical ends of the pathways. For example, the algorithms do not allow visualization of the subcortical portion of the front sections of the pyramidal tract [31]. Intersecting fibers in the semioval center are not visualized by DTI tractography due to reduction in fractional anisotropy at this location [32, 33]. It results in various artifacts and construction of false paths [28, 34]. In DTI tractography 1 voxel is equal to 1 fiber, which does not reflect the true number of axons in the voxel [35].

According to our data, the PT was intact in 7 (36.8%) of 19 patients with grade III—IV gliomas IV and metastases, and in 5 (50%) of 10 patients with brain gliomas of grade I—II. Tract infiltration with a tumor was observed in 2 (20%) of 10 patients with grade I—II gliomas and in 8 (42.1%) of 19 patients with grade III—IV gliomas and metastases. The PT was displaced in 3 (30%) of 10 patients in LGG subgroup and 6 (31.6%) of 19 patients in HGG and metastases subgroup. Thus, the DTI tractography data confirmed that the PT is more often involved in case of malignant tumors and allowed characterization of the degree of PT involvement in each case.

To prevent direct damage to the PT, direct subcortical electrical stimulation is used during the surgery, which allows

**Table 2. Data on extent of the tumor involvement with the PT structure**

<table>
<thead>
<tr>
<th>Hystology/Tumor-PT relationships</th>
<th>GRADE I</th>
<th>GRADE II</th>
<th>GRADE III</th>
<th>GRADE IV</th>
<th>MTS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrated</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Displaced</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>29</td>
</tr>
</tbody>
</table>
Figure 2. Spearman rank correlation: correlation between the tract status according to DTI tractography (0, intact; 1, displaced, 2, infiltrated) and neurological status before the surgery (preoperative muscle strength from 5 to 1 point).

The higher PT involvement in the tumor is, the more pronounced is the movement disorders before the surgery.

Figure 3. Gamma rank correlation: correlation between the proximity of the tumor to the tract according to DTI tractography (0, intact; 1, displaced, 2, infiltrated) and neurological dynamics after the surgery (1, positive trend with a partial regression of hemiparesis, 2, without substantial changes; 3, negative dynamics of reversible aggravation of hemiparesis, 4, negative dynamics with persistent aggravation of hemiparesis).

The closer the tumor is to the pyramidal tract, especially in case of infiltration, the higher is the risk of increase of motor disorders after the surgery.
identification of the PT fascicle a few millimeters before your approach them. The distance from the point of stimulation to the PT depends on both the stimulator (bipolar or unipolar) and the current strength and frequency. The foreign studies recommend reduction of the strength of the stimulating current in case of motor response during the direct ES. It limits the spread of the current into the tissues, allowing the surgeon to proceed with the removal of the tumor. Should lower current also results in a motor response, the surgery is stopped.

Different researchers use different strengths (from 2 to 10 mA) and amplitudes of the current for direct ES. K. Seidel et al. [36] propose to stop the resection of the tumor in case of response to stimulation with a current of 2 mA. Duffau N. et al. [37] also use the strength of 2 mA and consider direct ES safe, accurate and reliable for identifying pathways. J. Gonzalez-Darder et al. [38] note that the appearance of the motor response to stimulation with 3 mA current predicts irreversible damage (rupture) to the tract with a sensitivity of 83% and specificity of 95%. When low current strengths (1—3 mA) were used for direct subcortical ES, only 23 of the 67 patients did not present with permanent neurological disorders in the postoperative period, due to the large volume of resection in this category of patients [39]. It is known that the current strength is directly correlated to the distance over which it spreads, with a ratio of ca. 1 mm per 1 mA (“golden rule” of neurophysiology) [23, 40—42].

Most authors consider a distance of 10 mm between the PT and the edge of tumor to be “safe” one for preservation of motor function. J. GonzalezDarder et al. [38] considered 8—10 mm to be the safe distance with 70% of patients experiencing marked neurological deficit in the early postoperative period and 40% in the late period. According to G. Keles et al. [15], the corresponding figures for the operations in which the pyramidal tract was detected, were 27% for temporary deficit and 13% for permanent deficits. If the PT was not detected by direct ES during the surgery, the rate of aggravation of hemiparesis was 7.6% (temporary deficit) and 2.3% (permanent deficit). G. Carrabba et al. [43] adhere to 8 mm distance between the PT and the tumor, the rate of deficiency in the early post-operative period amounted to 59%, if PT was identified by the direct ES, and 10%, if it was not. In the late post-operative period, the rate of the deficit was 6.5% (PT identified during the surgery) and 3.5% (PT was not
Figure 6. Spearman rank correlation.
The impact of relationship of the tumor to the PT in patients with intact (0), displaced (1), and infiltrated (2) PT on the result of direct electrical stimulation during operation: 0, no motor response; 1, motor response. Motor responses at direct electrical stimulation occur significantly more often in case of displaced and especially infiltrated PT, according to DTI tractography.

Figure 7. Gamma rank correlation: relationship between the current strength (mA) at direct stimulation and neurological deficit in the postoperative period.
1, positive trend with a partial regression hemiparesis; 2, without substantial changes; 3, negative dynamics with reversible aggravation of hemiparesis; 4, negative dynamics with persistent aggravation of hemiparesis. The higher amperage required to obtain motor response by direct stimulation is, the farther the PT is from the point of stimulation, and the less likely is the damage and less pronounced is the negative neurological dynamics in the postoperative period.
identified), respectively. According to H. Duffau [44], in 95% of cases patients operated on for gliomas of eloquent areas of the brain had no neurological deficits on examination 3 months after surgery.

Our results have demonstrated that PT displacement and infiltration, based on the data of pre-operative DTI tractography, is significantly more often associated with:

a) responses to direct electrical stimulation during the surgery;
b) higher rate of neurological motor deficit prior to the surgery;
c) higher increase in neurological deficits after the surgery. It indicates high predictive value of PT and tumor visualization by DTI tractography prior to the surgery for both planning of the surgery and its actual performance.

The decline in or disappearance of responses to direct ES indicates damage to the PT and high probability of movement disorders in the postoperative period. According to our data, there is a significant correlation between the strength of the stimulation current used during the direct ES and neurological outcomes after the surgery: the higher the current, the better the motor outcomes, and vice versa. It can be explained by the fact that an increase in the current strength of the stimulus increases its depth of penetration (according to the “golden rule” of neurophysiology). As a result, the PT is identified at an earlier stage before it sustains any damage. However, even though neurological outcomes are better in this situation, the radicality of the surgery under direct stimulation with a higher current strength may by lower due to larger volume of the remaining tumor.

The preservation of the responses in case of direct ES does not always guarantee the absence of increase in neurological symptoms. It can be attributed to the fact that PT may be damaged above the stimulation site. In this case, TCMEP can be used to control the status of the paths and they can decrease or disappear altogether (decrease in the amplitude of M-response, increase in its latency) [45]. According to many authors [42], direct subcortical ES and TCMEP are complementary methods. Therefore, it makes no sense to see them as alternatives. However, the use of these methods during the surgery is associated with a number of regularities, which one can rely on, in order to access the degree of probability of increase in neurological deficit after the surgery. According to our data, the preservation of TCMEP during the surgery is a reliable predictor of lack of increase in neurological deficit in the postoperative period, which is consistent with the data of S. Ohue et al. [45]. Decrease in TCMEP amplitude during the tumor resection may indicate a direct contact with the PT or vascular damage.

<table>
<thead>
<tr>
<th>TCMEP dynamics/postoperative neurological deficit</th>
<th>No changes</th>
<th>Reduced responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hemiparesis worsening</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Hemiparesis worsening</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 4. Dynamics of intraoperative TCMEPs compared to the postoperative neurological status**

**Figure 8.** Spearman rank correlation: correlation between TCMEP during the surgery: 0, stable TCMEP, -1, decline in TCMEP and neurological dynamics in the postoperative period: 1, positive trend with partial regression hemiparesis; 2, without substantial changes; 3, negative dynamics with reversible aggravation of hemiparesis; 4, negative dynamics with persistent aggravation of hemiparesis.

Neurological motor outcomes are significantly better for stable TCMEP during the surgery.
If the PT has been partially damaged or there was a spasm of the vessels that feed the PT during the surgery, temporary increase in neurological symptoms can be expected afterwards. Expressed or irreversible neurological damage can occur in case of significant damage to the fascicle or a large vessel that supplies the tract. Several authors [42] considered the reduction in TCMEP amplitude by 50% from the baseline amplitude to be relatively safe level (threshold).

However, this method is not entirely accurate; it can produce false-negative results (some patients with reduced TCMEP had no expressed paresis after the surgery). This occurs for several reasons. Firstly, the electrodes may move due to the cut and tissue detachment in the surgical field. Secondly, TCMEP amplitude reduction may be caused by brain retraction due to removal of the tumor mass and CSF leakage, which leads to the formation of an air layer between the inner surface of the skull and the brain. In our view, a sharp decline in TCMEP amplitude and latency should alert the surgeon and serve as a signal for repeated direct stimulation in the operation area to confirm the proximity to the PT.

The development of postoperative deficiency is affected not only by the damage to the pathways, but also by a vascular factor. For example, coagulation of the anterior ciliary artery or lenticulostriate arteries may cause expressed hemiparesis. It should be noted that damage to a large vascular collector results in a rapid, complete and irreversible decline of TCMEP. Disruption of the PT function may also be due to other causes: 1) surgical traction; 2) overheating due to bipolar coagulation; 3) cytotoxic edema; 4) microvascular reorganization. In these cases, functional disorders occur even though the anatomical integrity of the PT is maintained [38]. Therefore, it is vitally important to monitor the integrity of the PT before removing the remainder of the tumor, rather than after the complete resection.

According to our data, TCMEP were stable in 17 out of 26 patients and 15 of 17 patients had no postoperative aggravation of hemiparesis. Decline in TCMEP amplitude was observed in 9 patients, of whom 7 had aggravation of hemiparesis after the surgery. The correlation between the preservation of TCMEP during the surgery and the neurological dynamics after the surgery is reliable. Thus, the preservation of TCMEP amplitude during the surgery is a reliable predictor of no aggravation of hemiparesis and motor deficits after the surgery, which is consistent with the data of S. Ohue et al. [23].

Therefore, the use of modern techniques of intraoperative neuronavigation in the surgery of brain gliomas located near the PT allows optimal planning of the surgery, permits a surgeon to be more confident in dealing with the deep structures in the brain and, if necessary, to quickly adjust the tactics of the intervention. Intraoperative neurophysiological research methods (especially combination of direct ES and TCMEP) play a special role in modern neurosurgery, allowing to identify...
the location of eloquent structures and conductive pathways of the brain, which makes it possible to minimize the risk of aggravation of neurological deficit in the postoperative period [46, 47]. However, each of these methods has its own limitations, advantages and disadvantages and should be used according to indications. The optimal outcome of intracerebral tumors surgery requires a multidisciplinary team of experts (neurosurgeon, neuroradiologist, neurophysiologist).

Conclusions

1. In case of direct electrical stimulation of the PT, motor responses were significantly more often observed for the pyramidal tract infiltrated and displaced by the tumor (according to preoperative DTI tractography).

2. Patients with the infiltrated or displaced pyramidal tract significantly more often had hemiparesis before surgery and aggravation of hemiparesis after the surgery compared to patients with the intact tract.

3. A reduction in the motor neurologic deficit in the postoperative period was significantly more often observed for application of a higher current strength during direct electrical stimulation.

4. Persistence of the TCMEP amplitude during the surgery is a reliable predictor for no aggravation of the motor neurological deficit after the surgery. Postoperative aggravation of hemiparesis was significantly more often observed when TCMEPs decreased during the surgery.

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Authors declare no conflict of interest.
REFERENCES


The work is dedicated to the surgery of the intracerebral tumors of the brain located near the pyramidal tracts. Information on topographo-anatomical relationships between the tumor and the pyramidal tract is crucial for surgeries of this type of lesions. These data can be obtained both preoperatively (using MRI tractography) and intraoperatively (using direct electrical stimulation). The cases of 29 patients with intracerebral tumors were analyzed and the use of transcranial electrical stimulation, its advantages and disadvantages were described in detail, demonstrating the advantages of the combined use of these methods.

The authors provide detailed analysis of their own and foreign experience in the surgical treatment of patients with gliomas located near the pyramidal tracts. The study is illustrated by clinical examples. The work is not without drawbacks, though. Unfortunately, the authors did not use intraoperative navigation to estimate the distance between the point of stimulation and the pyramidal tract. In general, the work seems relevant and useful for practicing neurosurgeons, neurophysiologists and neuroradiologists.
A Telescopic Vertebral Body Endoprosthesis for Subaxial Cervical Fusion

A.S. NEKHLOPOCHIN1, A.I. SHVETS1, S.N. NEKHLOPOCHIN2

1Lugansk State Medical University, Lugansk, Ukraine; 2Lugansk Regional Clinical Hospital, Lugansk, Ukraine

Purpose. The study’s purpose was to develop and implement into clinical practice an anterior subaxial cervical fusion technique using a new telescopic vertebral body graft (TVBG). Material and methods. We analyzed existing TVBGs used for anterior interbody fusion at the cervical spine level and developed our own variant of a vertical, cylindrical, telescopic, mesh, vertebral body endoprosthesis as well as a technique of cervical vertebral body replacement with the graft. The technique was used in 11 patients with vertebral-spinal injury. The orthopedic status, neurological status, and surgical treatment outcomes were assessed using ASIA/IMSOP, Odom, and Visual Analog Scale (VAS) scores. Results and discussion. The first cases of replacing a resected vertebra with the proposed graft indicate the applicability of TVBG for restoring the sagittal profile, stabilizing an operated spinal motion segment, and providing conditions for the formation of an adequate supporting bone block. The graft can be filled with a significant amount of a filler that can be added and tightened after placing the graft in the operating position. The study demonstrated the graft efficacy. There were no postoperative complications associated with telescopic prosthesis placement.

Keywords: subaxial cervical disorders and injuries, surgical treatment, telescopic prosthesis.

Abbreviations

ASIA — American Spinal Injury Association
IMSOP — International Medical Society of Paraplegia
VAS — visual analog scale
SMS — spinal motion segment
TVBG — telescopic vertebral body graft
CS — cervical spine

Anterior decompression, restoration of the sagittal profile, and stabilization are sufficiently effective and widespread surgical treatment for traumatic, degenerative-dystrophic, oncologic, and inflammatory lesions of the cervical spine (CS) [1, 2].

The anterior and middle supporting columns of the CS are mostly affected in traumatic injuries due to their anatomico-physiological, functional, and biomechanical features as well as the injury mechanism [3—5]. Metastatic and inflammatory processes in the CS are often localized in the vertebral bodies causing ventral compression of the dural sac. In most cases, intervertebral disc herniations and vertebral osteophytes associated with deforming spondylosis also cause compression of the anterior regions of the spinal neural structures. Because of this localization of the compression factor, decompressive-stabilizing surgery is performed using an anterior surgical approach as the most pathogenetically reasonable one in this case [1, 2, 6].

Analysis of many-year application of anterior autograft fusion as well as long-term surgical outcomes indicate that interbody fusion with a bone autograft alone is insufficiently effective [7, 8]. This is related to limited stabilizing capabilities of the technique. In these interventions, a graft displacement occurs in 29—68% of cases. Surgery-achieved correction is lost due to functional graft rearrangement in 5—10% of cases; consolidation fails in 33% of patients; kyphosis in the late injury period occurs in 38—64% of cases.

To eliminate these drawbacks typical of anterior interbody fusion using an autograft, improve qualitative characteristics, and optimize technique implementation, various vertical monoblock or telescopic vertebral body grafts (TVBGs) made of synthetic materials and bioinert metals and their alloys are used in clinical practice [6, 9].

At the same time, anterior interbody fusion using a metal TVBG has certain peculiarities that are associated with the elasticity modulus differences between bone structures of the vertebral bodies and a metal, design features, and functionalities of grafts [10].

The processes occurring in the metal — bone system under compressive stress condition can lead to bone tissue resorption, graft migration, and sagittal imbalance as well as can cause compression of the spinal cord, its roots, and sheaths. These complications can develop both in the early and late postoperative periods [11, 12].

As a result, the efficacy of TVBG-based anterior fusion depends on the bone block strength properties associated with the graft cavity size available for a filler in the graft — vertebral body system [13].

The CS is divided, based on the anatomical and functional features, into the atlanto-axial (C1—C2) and subaxial (C3—C7) levels. The problem of configuration optimization of TVBGs used in surgical interventions at the subaxial level is topical due to small size of a bone defect for TVBG placement and a wide range of CS movements, which defines quite strict requirements for the technical and functional characteristics of grafts.

The study’s purpose was to develop and implement into clinical practice an anterior subaxial cervical fusion technique using a vertebral body graft.
Material and Methods

We performed a comparative analysis of the structural characteristics of various TVBGs used in anterior fusion at the CS level [14, 15]. The CS stress-strain state features associated with replacement of vertebral bodies with artificial grafts of a different design were simulated in the Biomechanics Laboratory at the Sitenko Institute of Spine and Joint Pathology (Ukraine).

The vertical, cylindrical, telescopic, mesh vertebral body endoprosthesis was developed based on the computer simulation results. The optimal graft configuration was determined with allowance for the anatomical and biomechanical features and injury nature of the CS, physical properties of bone tissue, a graft filler, and graft material, and also technical, functional, and mechanical characteristics of an endoprosthesis (patent of Ukraine #96368, Vertebral endoprosthesis “LAS”, of 10.02.15. Clinical applications of the developed vertebral body endoprosthesis were approved by the Ethics Committee of the Lugansk State Medical University, protocol #2 of 14.03.13).

We performed an analysis of the treatment outcomes in 11 patients (10 males and 1 female; mean age 32.7 years (ranging from 18 to 61 years)) who underwent ventral subaxial cervical fusion for traumatic CS injury using the developed graft (Inmasters, Khar’kov, Ukraine) at the Neurosurgical Department in the period from March to November 2013.

All patients were subjected to X-ray imaging in two planes and computed tomography before and after (3—5 days and 3, 6, and 12 months) surgery. Clinical treatment outcomes were analyzed using the listed below scales of changes in the cervical lordosis and sagittal profile. The relationships in a graft — vertebral body complex were determined based on measurement of the interbody space in an operated segment postoperatively and 10—12 months after surgery. The degree of lordosis was matched to the axis angle according to a method proposed by V.T. Pustovoytenko et al. (the axis angle is composed of two lines: a line connecting the postero-inferior angles of the C2 and C7 vertebrae and the central axis line. Hyperlordosis is characterized by an angle of 26—36°, normal lordosis by an angle of 19—25°, mild (smoothed) lordosis by an angle of 13—18°, straightened cervical lordosis by an angle of 10—12°, and kyphosis by an angle of 1—9° and minus 1—12° [16].

The orthopedic and neurological status and surgical treatment outcomes were assessed using ASIA/IMSOP, Odom, and VAS scores [17—20].

The efficacy of achieved spinal fusion was assessed based on a series of qualitative and quantitative features. The qualitative features were as follows:
• elimination of the risk for intraoperative and postoperative compression of the neural structures due to avoiding a TVBG dislocation into the spinal canal lumen;
• no signs of destruction and dislocation of an implanted system and its components with loss of intraoperative correction of the sagittal profile;
• no signs of damage and structural changes to bone tissues of the vertebral bodies being in contact with fixation elements of the system.

The quantitative criteria included indicators, such as the axis angle and height of an operated spinal motion segment.

Results

Endoprosthesis design

A telescopic vertebral body endoprosthesis is a hollow shaft with an oppositely directed thread coming from the center. Half shells with teeth on their ends equipped with L-shaped plates having paired screw holes are screwed on the thread. The shaft and half shells have through holes arranged in tiers. Under L-shaped plates, the half shells have functional holes for adding a filler into the prosthesis after its placement in a bone defect.

The developed prosthesis is different from its analogues in several features (Fig. 1):
• has the minimum size required to perform anterior fusion at the subaxial level;
• has a larger cavity compared to that in other devices. The cavity is maximally filled with autologous bone chips made of the iliac wing and with hydroxyapatite or alumina ceramic granules, which provides a larger contact area in the filler — vertebral body system to ensure conditions for adequate bone block formation (a letter #18 MB-3169 of the Ministry of Healthcare of Ukraine “On monitoring of the quality, safety, and production of pharmaceuticals and healthcare products” approved clinical trial of these materials);
• has sufficient strength, low metal content, and low weight since it is a hollow cylinder with a threaded connection between half shells and an inner socket, i.e. it is an axially symmetric construction. Compressive stress is distributed over the entire graft cross-section, which enables relatively thin wall systems to withstand sufficiently high compressive stress;
• excludes damage to the endplates by teeth of end surfaces during placement in the operating position;
• is easy-to-fabricate and easy-to-use.

Figure 1. Endoprosthesis design.
The endoprosthesis is fixed to the vertebral bodies adjacent to a resected one by monocortical screws, and no extra fixation by a ventral plate is required.

**Surgical technique**

Surgeries were performed through a ventrolateral approach, with partial or total resection of an affected vertebral body, removal of the adjacent intervertebral discs and, if necessary, posterior longitudinal ligament, and exploration of the epidural space.

The endoprosthesis (prefilled with autologous bone chips or a mixture of autologous bone chips and granules of other fillers) is placed in the initial position in a bone defect formed after removal of an affected vertebral body. The graft is deployed by shaft rotation, thereby eliminating a sagittal deformity of the cervical spine and restoring the spinal segment height. An increase in the graft height results in filling defects between the vertebral bodies adjacent to a resected vertebra and an endoprosthesis filler. The defects are eliminated by addition of filler granules through special functional holes. L-shaped plates of half shells have holes for prosthesis fixation, using cortical screws, to the superjacent and subjacent vertebral bodies. The thread is deformation locked to avoid graft twisting decreasing the defined vertical size.

A Philadelphia collar was used in the postoperative period for CS fixation for 2.5—3.0 months.

**Table 1** provides information on neurological disorders in patients (classified by using the ASIA/IMSOP scale at admission to the hospital) as well as on injuries of the spinal osteoligamentous complex, classified according to C. Argenson (1994) [21].

At admission to the hospital, patients with wedge compression fractures of the vertebral bodies (according to the ASIA/IMSOP scale) presented with neurological symptoms typical of group D (1 case, 9.1%) and group E (1 case, 9.1%). Severity of a neurological deficit in patients with burst vertebral body fractures was assigned group D in 1 (9.1%) case and group E in 2 (18.2%) cases. Patients with comminuted vertebral body fractures of the “hanging drop” type were assigned group B in 1 (9.1%) case and group C in 1 (9.1%) case. Patients with bilateral fracture-dislocations were included in groups D (1 case, 9.1%) and E (2 cases, 18.2%). One (9.1%) patient had a simple avulsion fracture of the articular pillar (group E).

Analysis of the patients’ neurological status within 12 months after surgery demonstrated positive changes, as evidenced by the data shown in **Table 2**, according to which 1 (9.1%) patient moved from group B to group E, and 2 (18.2%) patients moved from group D to group E. Therefore, neurological symptoms regressed in 3 out of 5 cases. There were no changes in 2 cases, which was likely associated with irreversible traumatic lesions of the spinal cord and its roots.

In the preoperative period, the axis angle was –3° (4 to –10°), on average; the defect height of an operated SMS was 9.34 mm (range of 6—17 mm), on average.

After surgery using the endoprosthesis, the axis angle range was 20—23°; the height of an operated spinal segment remained at an average level of 17.4 mm and 17.3 mm postoperatively and 10—12 months after surgery, respectively. An analysis of tomograms and spondylograms revealed no signs of spine fusion failure for the entire follow-up period.

According to the VAS, pain syndrome in the operated patients was reduced from 6—8 to 3—4 points by the 3rd month. This indicator amounted to 1—3 points on month 6 and reached 0—1 points by the 12th month.

The clinical outcomes of anterior fusion were evaluated according to the Odom criteria that are based on subjective sensation of surgery-associated changes in the condition and on the physical activity level. The results were regarded as satisfactory in 2 cases, as good in 5 cases, and as excellent in 2 cases; there were no changes in 2 cases.

---

**Table 1. Characterization of neurological disorders and injuries of the CS osteoligamentous complex**

<table>
<thead>
<tr>
<th>CS injury</th>
<th>Severity of spinal cord injury</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Compression injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>9.1</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion-distraction injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotational injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Changes in the neurological status of operated patients (ASIA/IMSOP scale)**

<table>
<thead>
<tr>
<th>ASIA/IMSOP scale</th>
<th>3—5 days</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Group B</td>
<td>1 (9.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group C</td>
<td>1 (9.1%)</td>
<td>2 (18.2%)</td>
<td>1 (9.1%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Group D</td>
<td>3 (27.3%)</td>
<td>2 (18.2%)</td>
<td>2 (18.2%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Group E</td>
<td>6 (54.6%)</td>
<td>7 (63.7%)</td>
<td>8 (72.8%)</td>
<td>9 (81.9%)</td>
</tr>
</tbody>
</table>
No complications were observed in both the early and late postoperative periods.

The results of clinical observation and analysis of tomograms and spondylograms of all patients (3, 6, and 12 months after surgery) clearly demonstrate pronounced positive neurological changes, regression of functional disorders in operated patients, and preservation of intraoperative correction of the CS sagittal profile.

Here, we present clinical cases of bisegmental (Fig. 2) and multisegmental (Fig. 3) interbody fusion using a TVBG.

Discussion

Currently, anterior interbody fusion using a TVBG is one of the most effective techniques of sagittal balance restoration and operated SMS stabilization in decompressive-stabilizing or reconstructive surgery of the anterior and middle supporting columns of the spine.

A variety of grafts differing in their design are available for spinal surgeons. TVBGs used in clinical practice are far from perfect and, therefore, along with advantages, have technical disadvantages affecting their functionality.

For example, Mesh and telescopic (ADD, ADDplus, BodyVertEx, TeCorp, Monolith, ECD, TPS) grafts are mainly used for anterior fusion at the CS level.

Each of the listed vertebral systems has its structural and functional features. For example, the Mesh endoprosthesis has a large cavity for a filler designed to form a bone block and performs well the reconstructive function. However, the endoprosthesis is used in combination with a ventral plate [22].

ADD and TeCorp grafts successfully serve for the reconstruction purposes. Their use is associated with extra SMS stabilization due to additional fixation with a ventral plate [23].

Furthermore, the filler cavity size is restricted because the expandable mechanism of these TVBGs is located inside the device and is insufficient to form a supporting bone block [24].

New generation stabilizing systems (ADDplus, BodyVertEx, and Monolith) are effective for SMS reclamation and stabilization and enable sagittal profile correction and SMS stabilization without using ventral plates. At the same time, they do not usually provide conditions for the effective bone block formation, which is essential for preserving intraoperative correction of the spinal motion segment in the late postoperative period [25].

Of particular interest is a TPS graft that efficiently combines the maximum contact area in metal — bone and material — bone systems. Its design enables material tightening in the vertebral body contact area, following placement in a bone defect and SMS reclamation. However, some disadvantages of the device should be noted, namely:

1) not-easy-to-fabricate;
2) a high cost due to design features;
3) a large vertical size of the assembled TVBG may hinder its installation in the interbody space;
4) coaxial grafts, unlike TPS systems, are more efficient and reliable in terms of tolerance to compressive stress due to an even stress distribution;
5) coaxial devices are less metal consuming compared to TPS-like systems;
6) large holes on the side surfaces may complicate tight filling of the inner cavity with autologous bone fragments and hydroxyapatite ceramic granules before placing the device in a bone defect.

The listed design features of TPS-like systems make them unaffordable for patients due to a high cost [26]. Their effectiveness in preserving achieved intraoperative correction of the sagittal profile is not sufficient due to a potential deformation. The TVBG design features restrict the capabilities for bone block formation by filler tightening after placing the endoprosthesis in a bone defect and for SMS reclamation.

We consider telescopic systems as the most effective and perfect devices in restoration of the anterior support. They optimize the process of sagittal profile correction due to the opportunity of graduated changing the distance between the vertebrae adjacent to resected ones, which is the main advantage
of these systems that enables full implementation of the surgical tasks [27, 28].

Thus, the presented functional features and disadvantages of the described TVBGs used for anterior subaxial cervical fusion necessitate further studies on optimization and improvement of the graft design.

Conclusion

The first cases of replacement of a resected vertebra by the described prosthesis suggest the advisability of this TVBG for restoration of the sagittal profile and stabilization of an operated SMS. The graft cavity size enables its filling with a significant amount of autologous bone or its substitutes, while the structural features make it possible to add and tighten a filler, following graft placement and fixation to initiate osteogenesis and provide conditions for bone regeneration.

Our small series of clinical cases showed a good efficacy of the new prosthesis in sagittal profile restoration, operated SMS stabilization, and formation of an adequate supporting bone block.

Authors declare no conflict of interest.

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Anterior decompression is a must in the case of support function abnormalities of the anterior and middle columns of the spine typical of traumatic and pathological vertebral body fractures associated with tumor, infection, or osteoporosis. The use of grafts to provide optimal spine fusion conditions has extended the amount of manipulations and radicalness of treatment for spinal tumors. Numerous studies on this topic demonstrate the advantages of corpectomy compared to laminectomy in the case of nerve structure compression or deteriorating spinal deformity. Many authors also note a high efficiency of spine sagittal balance reconstruction and spine fusion quality associated with implantation of hollow vertebral body prostheses. The use of hollow mesh and expandable implants is routine in modern neurosurgical practice; however, telescopic models increase the overall cost of a stabilizing device, and many modifications deprived of a filling cavity are doubtful in terms of the adequate spinal fusion formation, following circular decompression at the spinal motion segment level. Therefore, the most popular system is a Mesh hollow implant, which is used together with a ventral plate.

However, given the permanent entry of new devices into the market of grafts for spine stabilization, the present work is of special significance.

This article describes in detail a variety of grafts used for reconstruction of the anterior and middle supporting columns of the spine. The authors divided modern implants according to the supporting properties and implantation mechanism and described the objective reasons for choosing an implant in a particular case. Thus, this paper is a review that provides essential information for neurosurgeons, traumatologists, orthopedists, and oncologists who are commonly faced with the need for spine reconstruction.

In addition, the authors presented their own invention — an endoprosthesis for reconstruction of the anterior and middle supporting columns of the cervical spine. A distinctive feature of this implant, in addition to a cavity filled with material for spinal fusion formation, is deformation thread locking.

At the same time, there is no detailed description of the method of graft placement. In addition, the patent for the invention is in Ukrainian, without a translation into Russian or English, and not accompanied by a reference, which complicates its search on the Internet. These drawbacks make this paper a little bit unfinished.

N.A. Konovalov, V.A. Korolishin (Moscow, Russia)
Results of Surgical Treatment of Syringomyelia Associated with Chiari 1 Malformation. An Analysis of 125 Cases

A.A. ZUEV, N.V. PEDYASH, D.S. EPIFANOV, G.V. KOSTENKO

Pirogov National Medical Surgical Center, Moscow, Russia

The rate of Chiari malformation (CM) ranges from 3 to 8 per 100,000 population. In 62—80% of cases, CM is accompanied by the development of syringomyelia (SM) at various levels. The clinical picture in these patients is a combination of CM and SM manifestations. However, SM symptoms often prevail, which creates some problems in the disease diagnosis and in the choice of optimal treatment. Objective. On the basis of our own experience of surgical interventions, we aimed to clarify the indications for surgical treatment of SM associated with CM and to define the optimal extent of surgery and criteria for evaluation of treatment outcomes. Material and methods. Two hundred twenty-five patients with a combination of syringomyelia and Chiari 1 malformation were examined in the period from 2011 to February 2015. Of them, 125 patients were operated on. The mean age of the operated patients was 56±8 years. The mean time from the appearance of the first signs of the disease to surgery was 75±82 months. All operations were performed by a single surgeon. All operations were carried out with the patient in the semi-sitting (89.6%) or prone (10.4%) position. The operation included sparing suboccipital craniectomy, C1 arch resection, restoration of cerebrospinal fluid (CSF) circulation along the posterior surface of the cerebellum, and reconstruction of the dura mater (DM) in the craniovertebral junction region. Results. Exploration of the arachnoid mater of the cisterna magna after dura opening revealed no arachnopathy in 78 (62.4%) patients (Chiari 0 malformation according to Klekamp). Type 1 arachnopathy (by Klekamp) was detected in 31 patients (24.8%), and type 2 arachnopathy was observed in 16 (12.8%) cases. The condition of 109 (88%) patients was evaluated one year after the surgery. Sixty one (56%) patients had partial or complete regression of the preoperative neurological symptoms. The disease stopped progressing in 44 patients (40%). The disease was worsened in 4 (3.7%) patients. No recurrence of a CSF circulation disturbance at the craniovertebral level was observed during follow-up. Early postoperative complications occurred in 4 (3.2%) patients: wound CSF leakage in 1 (0.8%) patient, acute epidural hematoma in 1 (0.8%) patient, and aseptic meningitis in 2 (1.6%) patients. Temporary deteriorations in the condition (headache worsening, meteosensitivity) were detected in 11 (8.9%) patients. The symptoms regressed by the end of the 1st postoperative month. There were no deaths. Conclusions. The indication for surgery in patients with a combination of CM and SM is the presence of neurological symptoms associated with syringomyelia and their progression as well as headache caused by herniation of the cerebellar tonsils that significantly deteriorates the patient’s quality of life. The main criteria for evaluating the treatment efficacy include stabilization of the clinical symptoms and/or an improvement in the patient condition. Suboccipital craniectomy followed by DM reconstruction and restoration of CSF circulation in the craniovertebral region is an effective treatment for syringomyelia associated with Chiari 1 malformation.

Keywords: syringomyelia, Chiari malformation, CSF circulation, suboccipital decompressive craniectomy.

Chiarini malformation (CM) and syringomyelia (SM) are two diseases that occur independently of each other. However, they often occur in combination, which may fundamentally change the treatment strategy. According to various authors, the CM rate ranges from 3 to 8 per 100,000 population; in 62—80% of cases, CM is accompanied by the development of SM at various levels of the spinal cord. The clinical picture in these patients is a combination of CM and SM manifestations. However, the SM symptoms often prevail, which creates some problems in the disease diagnosis and in the choice of optimal treatment.

To date, various approaches for treating these diseases have been reported in the literature that are based on theories explaining causes of the SM development and progression. However, none of the theories can fully explain all clinical and pathophysiological aspects of this condition. Therefore, further investigation of the pathogenesis of cyst formation in the spinal cord is required. The most popular and widespread theory of development of CM-associated SM is a theory by W. Gardner (1950) that is based on the assumption that obstructed CSF outflow from the cisterna magna into the spinal subarachnoid space leads to hydrodynamic shocks of the CSF systolic wave from the IVth ventricle to the central canal walls, which results in the canal expansion and formation of a syringomyelic cavity. On this basis, restoration of CSF circulation in the craniovertebral junction region is the main goal of surgical treatment. However, there are various unresolved problems in this field: what are the symptoms for choosing a surgical technique; what treatment outcomes should be considered satisfactory; how to treat patients with CM, SM, and basilar impression, etc.

On the basis of our own experience of surgical treatment of these patients, we tried to define the optimal extent of surgery and criteria for assessing treatment outcomes and to answer some arisen questions.

Material and Methods

A total of 225 patients with a combination of syringomyelia (SM) and Chiari malformation type 1 (CM1) were examined in the period from 2011 to February 2015. Of them, 125 patients (52 males and 73 females) were operated on. The indication for surgery in all patients was the presence of neurological symptoms associated with SM, their progression, and headache caused by cerebellar tonsillar herniation that significantly deteriorated the patients’ quality of life. The presence of CM and SM in the absence of clinical manifestations of the diseases was not an indication for surgery, regardless of the depth of...
cerebellar tonsillar herniation as well as the size and localization of a syringomyelic cyst. These patients received supportive conservative treatment and were followed-up (100 patients in our study).

The mean age of operated patients was 56±8 years; the mean time from the appearance of the first signs of the disease to surgery was 75±82 months. A thorough neurological examination of the patients was carried out before surgery; postoperative examinations were performed every 6—12 months. The maximum follow-up duration was 3.8 years; the minimum duration was 6 months (median, 1.4 years). The disease manifested as dissociative disorders of sensation in 65% of patients, cervico-occipital pain in 37.1% of cases, pyramidal symptoms in 8.9% of cases, and hypertension symptoms in 1.6% of patients. Most patients had all of the listed symptoms at the time of hospitalization. All patients underwent preoperative MRI of the brain and entire spinal cord; further examinations were performed every 6—12 months. Some patients with a concomitant craniovertebral region anomaly (basilar impression, platybasia, C1 assimilation, etc.) underwent computed tomography (CT).

Preoperative phase-contrast MRI with cardiac synchronization was conducted in 23 (18.4%) patients. This examination was needed to confirm a block of CSF flow in the craniovertebral region. The examination was especially indicated for patients who had previously undergone decompression in order to decide whether the repeated procedure was advisable.

All operations were performed by a single surgeon with the patient in the semi-sitting (89.6%) or prone (10.4%) position. A 4—5 cm skin incision in the occipital region was followed by suboccipital craniectomy of up to 3 cm in diameter and C1 laminectomy (Fig. 1).

The dura mater was opened with a Y-shaped incision. The arachnoid mater of the cisterna magna was maximally preserved during DM opening. Then, DM was inspected for adhesions. If arachnopathy (type 1 and 2, by Klekamp [11]) signs were detected, the cisterna magna was opened, adhesions between the arachnoid mater and the cerebellum, medulla oblongata, and spinal cord were dissected, CSF circulation along the posterior surface of the cerebellum was restored, and the foramen of Magendie was inspected (Fig. 2).

In patients with pronounced arachnoid scars, scar dissection was limited to the midline to provide a connection between the intracranial subarachnoid space and the spinal cord space. Adhesions on the lateral surface of the medulla oblongata and spinal cord were not dissected to avoid damage to the structures or small blood vessels (Fig. 3).

If the cerebellar tonsils descended to the C2 level and below, the tonsils were subpially resected. At this stage, some patients who had isolated dilation of the fourth ventricle were implanted with a shunt going from the IVth ventricle through the foramen of Magendie (most often obliterated by adhesions in this situation) to the subarachnoid space of the cisterna magna. Then, reconstruction of the dura mater in the craniovertebral junction region was performed. For this purpose, we used artificial dural substitutes (Gore, DuraForm, SeamDura, DuraPair, etc.) in all patients. This material was used to reduce the risk of recurrence of CSF circulation disturbances due to postoperative adhesions between the dura mater and the cerebellar surface. Some patients with an appropriate thickness of the occipital bone underwent reconstruction of a defect with a titanium implant. This reduced the adhesion process outside the dura mater and eliminated compression of the arachnoid space by swollen muscles (Fig. 4).

Particular attention was paid to careful muscle suturing. A small, 4—5 cm, incision, not reaching the external occipital protuberance, allowed for complete wound sealing with a muscular layer.

In the early postoperative period, most patients underwent brain MRI to rule out hemorrhagic and ischemic foci. Further examinations were carried out after 4—6 months, 6—12 months, and then annually. The clinical symptoms and surgical treatment outcomes were evaluated in the same period. Because

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**Figure 1.** The extent of adequate bone resection for Chiari 1 malformation. A CT scan of the skull bones and subsequent 3D reconstruction.
Adhesiotomy (type 2 arachnopathy) and detachment of DM from the brain along its posterior surface (indicated by red arrows) were performed. The foramen of Magendie is opened, a ventriculocisternal shunt is placed through the foramen into the IVth ventricle cavity (blue arrow).

progression of clinical disease symptoms was the indication for surgery, treatment outcomes were considered as satisfactory in the case of stabilization or improvement of the patient’s condition.

Results

Chiari 1 malformation is often associated with other malformations of the craniovertebral region. In our series, apart from the descended cerebellar tonsils, 56 (44.8%) patients had hyperostosis of the occipital bone, platybasia, basilar impression, C1 assimilation, and a Klippel-Feil anomaly.

Exploration of the arachnoid mater of the cisterna magna after dura opening revealed no arachnopathy in 78 (62.4%) patients (Chiari 0 malformation according to Klekamp); thus, no opening of the arachnoid mater was required. Type 1 arachnopathy (by Klekamp) was detected in 31 patients (24.8%), and type 2 arachnopathy was observed in 16 (12.8%) cases. These patients underwent dissection of adhesions and restoration of CSF circulation along the posterior surface of the cerebellum and spinal cord. In 12 (9.6%) cases, isolated dilation of the IVth ventricle required forth ventriculosubarachnoid shunting. The cerebellar tonsils were resected in 6 (4.8%) patients if the tonsils descended to the C2 level and below and significantly impeded CSF circulation.

Two (1.6%) patients with concomitant hydrocephalus underwent, apart from suboccipital decompression, one-stage ventriculoatrial shunting and the major surgery.

Two (1.6%) patients with concomitant basilar impression underwent one-stage transnasal endoscopic resection of the dens, suboccipital craniectomy, C2 arch resection, and occipitopondylosis.

Control MRI 4 months later revealed that SM resolved in 19 (15.3%) patients, decreased in 89 (71.8%) cases, and remained unchanged in 16 (12.9%) patients (Fig. 5 and 6).

The condition of 109 (88%) patients was evaluated one year after the surgery (77 patients were present, while the condition of the remaining 32 patients was evaluated remotely). A total of 61 (56%) patients had partial or complete regression of the preoperative neurological symptoms. The disease stopped progressing in 44 (40%) patients. The disease was worsened in 4 (3.7%) patients only. Cardiac-synchronized phase-contrast MRI of the craniovertebral junction region was performed in these patients 4—12 months after suboccipital decompression to evaluate CSF circulation. No signs of a CSF flow block were detected. Therefore, the patients underwent
syringosubarachnoid shunting for stabilization of neurological symptoms (Fig. 7).

No recurrence of CSF circulation disturbances at the craniovertebral level was observed in the operated patients during follow-up.

Early postoperative complications occurred in 4 (3.2%) patients: 1 (0.8%) patient had wound CSF leakage; 1 (0.8%) patient had an acute epidural hematoma; and 2 (1.6%) patients had aseptic meningitis (DM in both patients was reconstructed with a dural substitute of the same brand). Temporary deteriorations (headache worsening, meteosensitivity) were observed in 11 (8.9%) patients. These symptoms regressed by the end of the 1st postoperative month.

Pseudo-meningocele signs, which were not accompanied by any neurological symptoms and cosmetic disturbances and did not require changes in the treatment approach, were detected during control MRI of the brain in 3 (2.4%) patients.

There were no deaths.

Discussion

Given the affordability of MRI in our country, diagnostics of CM and SM is not problematic. However, these conditions are often overdiagnosed. This is due to the fact that, to date, the value of a clinically significant displacement of the cerebellar tonsils is still disputed. According to most experts, a 5 mm or larger displacement in adult patients is considered as pathology, whereas this displacement may be physiological in children due to cerebellum growth. A disturbance of CSF circulation at the craniovertebral level can also be caused by a bone abnormality in the absence of a cerebellum displacement (Chiari malformation type 0, first described by B. Iskandar in 1998 [4—6]). In these controversial cases, phase-contrast MRI and assessment of CSF circulation in this region are recommended [7].

Given the diversity of disease clinical manifestations, it is important to identify the main symptoms and assess their dynamics. According to many authors, the presence of CM andpronounced SM in the absence of clinical symptoms and signs of disease progression is not an indication for surgery.

Despite the fact that suboccipital decompression is widely used for treating CM1, there is no generalized algorithm of this manipulation. Surgery proposed by W. Gardner included extensive craniectomy of the posterior fossa, opening of the IVth ventricle, and plugging the obex with a piece of muscle; the dura mater was not closed. The author reported five fatalities after 74 operations. Similar rates of postoperative mortality and patient condition deterioration have had other surgeons to use less invasive procedures, such as preservation of the intact arachnoid mater after dura opening, incision of only the outer dura layer, or bone decompression alone. In our opinion, the optimal and most accepted surgical technique is that described above. However, the decision on the extent of surgery is made by the neurosurgeon for each particular case based on the disease pathogenesis in a particular patient. Availability of MRI scans enables analyzing disease, allowing for all anatomical peculiarities, and planning surgery. The complexity of decision making is related primarily to the rarity of these diseases.

We used only artificial dural substitutes for DM reconstruction. In our opinion and according to J. Klecamp,
this reduces the risk of recurrence of CSF circulation disturbances in the craniovertebral region due to adhesions.

According to the modern concepts, drainage of a syringomyelic cyst is a temporary symptomatic procedure. This operation may cause secondary fixation of the spinal cord and SM, and, therefore, it should be used as rarely as possible. In our series of observations, this procedure was required only in 4 patients with SM progression. A decision on syrinx shunting should be made no earlier than 4 months after suboccipital decompression. In the case of normalization of CSF circulation at the craniovertebral level, this time is enough to evaluate clinical symptoms that are the main criterion for the assessment of treatment results. Despite adequately performed decompression, a syringomyelic cyst may not change or reduce for this period.

The disease rarity and, as a result, low awareness of neurologists and neurosurgeons on its pathogenesis, treatment options, and possible outcomes lead to the situation where some patients are not operated on for years and, finally, become profoundly disabled. On the other hand, we often face consequences of undue surgeries performed in the absence of indications for them or surgeries performed incompletely. As a result, some doctors conclude inoperability or meaninglessness of surgical treatment. As our study shows, identification of the indications for surgery and appropriate surgical treatment provide good outcomes with the minimum complication rate and zero mortality in more than 90% of patients.

**Conclusion**

A set of surgical procedures, including suboccipital craniectomy, C1 arch resection, and subsequent DM reconstruction and restoration of CSF circulation in the craniovertebral region, which are performed on time and according to indications, is an effective approach for treatment of SM associated with CM1.

The indications for surgery include the presence of SM-associated neurological symptoms, their progression, and/or headache caused by herniation of the cerebellar tonsils and significantly deteriorating the patients’ quality of life.

The essential extent of surgery includes economic resection of the occipital squama (up to 3 cm), C1 arch resection, exploration of the subarachnoid space of the cisterna magna, and dissection of arachnoid adhesions, if present, for restoration of CSF circulation along the posterior surface of the cerebellum, followed by expansive DM reconstruction using artificial dural substitutes in the craniovertebral junction region.

The main criteria of the treatment efficacy in patients with combined pathology, CM1 and SM, include stabilization of the clinical symptoms and improvement of the patient condition.

**Authors declare no conflict of interest.**
The article presents a clinical study of outcomes of surgical treatment in 125 patients with a combination of Chiari malformation and syringomyelia performed in the period between 2011 and 2015. The indication for surgery included neurological symptoms associated with syringomyelia, their progression, and also headache resulting from cerebellar tonsillar herniation and significantly affecting the patient’s quality of life. The authors performed a detailed analysis of the clinical and MRI semiotics of this group of patients and described a surgical technique that typically involved suboccipital craniectomy of the foramen magnum (about 3 cm in diameter) and C1 laminectomy, a Y-shaped incision of the dura mater with subsequent exploration of the arachnoid mater and evaluation of arachnopathy severity (according to Klekamp), which was the basis for deciding on opening the cisterna magna. If the cerebellar tonsils descended to the C2 level and below, subpial resection of the tonsils was performed. All patients underwent DM reconstruction in the craniovertebral junction region using artificial dural substitutes (Gore, DuraForm, SeamDura, DuraPair, etc.). Some patients were also implanted with syringosubarachnoid and ventriculosubarachnoid shunts.

The condition of 109 (88%) patients was evaluated one year after the surgery. The disease stopped progressing in 44 (40%) patients; 61 (56%) patients had a partial or complete regression of the preoperative neurologic symptoms. The disease was progressing only in 4 (3.7%) patients. Control MRI 4 months later revealed that syringomyelia disappeared in 19 (15.3%) patients, decreased in 89 (71.8%) cases, and remained unchanged in 16 (12.9%) patients. The authors also evaluated the rate of postoperative complications, which was 3.2%. The authors conclude that suboccipital craniectomy, C1 arch resection, and subsequent DM reconstruction and restoration of CSF circulation in the craniovertebral region, performed on time and according to the indication, to be an effective treatment for syringomyelia associated with Chiari malformation type 1.

In our view, this work is a valuable and topical study since it presents a detailed description of the data obtained in a large, for domestic literature, group of 125 patients. Also, high quality of acquisition of the epidemiological and clinical data should be mentioned. A significant achievement of the study is unification of the indications for surgery, surgical technique, and approach for postoperative data analysis. Thus, the authors demonstrated the efficacy of surgical treatment in a rather homogeneous group of patients. The technical aspect of performed interventions does not raise any questions since the intervention is based on the classic approach to surgery for Chiari malformation, which not raise any questions since the intervention is based on the classic approach to surgery for Chiari malformation, which
months after operations and a low rate of complications indicate high expertise and surgical skills of the authors.

Thus, most questions to the article are not methodological but rather conceptual and are related to the ambiguity of approaches to surgical treatment for Chiari malformation.

For example, the authors performed reconstruction of the dura mater in all patients, without exception. This is the rule of thumb approach, but if it is pathogenetically reasonable in all cases? In our practice, we routinely use ultrasound to decide whether dura reconstruction is required. We believe that a noninvasive examination of volume relationships in the craniovertebral region as well as of CSF circulation and the blood flow velocity in the straight sinus using transcranial dopplerography is a highly effective and safe method to identify preoperatively a leading pathophysiological syndrome (compression, CSF circulation, or mixed type disturbance). Identification of this syndrome in the clinical diagnosis provides the surgeon with information about a possible surgical approach: DM reconstruction using a dural autograft (local aponeurotic flap) is suitable in the case of obstructed CSF circulation and mixed disturbances, while bone decompression is essential in the case of compression disorders. Intraoperative ultrasound allows ensuring the adequacy of decompression and, if necessary, modifying an intervention approach. Probably, evaluation of this parameter would enrich the study with practical information.

The use of shunt surgery in patients with syringomyelia is associated with some questions. According to the monograph “Syringomyelia” by Jörg Klekamp, an acknowledged leader in the treatment of CSF circulation disorders, the failure rate of syringosubarachnoid and ventriculosubarachnoid shunting in patients with syringomyelia and arachnopathy is 92—100%; at the same time, Klekamp says that the technique can be used in particular cases (apparently, the authors were guided by this note). It would be interesting to give more attention to the efficacy/inefficacy of shunting in the present study.

Finally, the surgical technique used by the authors is also debatable. For instance, in our practice, we often use endoscopic techniques, including flexible endoscopy of the subarachnoid space (thecaloscopy), endoscopic cyst fenestration, and an endoscopic portal approach to the foramen magnum in some cases. Undoubtedly, the choice of a surgical technique is the exclusive prerogative of the surgeon, and this is why the uniform surgical approach used in the study is both an advantage and disadvantage of the work.

Thus, we believe that the article “Results of surgical treatment of syringomyelia associated with Chiari 1 malformation. An analysis of 125 cases” to be topical and highly informative work. The issues that it raises are absolutely reasonable and reflect the complexity and diversity of common pathologies, such as Chiari malformation, syringomyelia, and arachnopathy. Discussions in the neurosurgical society induced by similar studies should encourage us for generalization of the available data and continuous analysis of surgery outcomes.

A.O. Gushcha, A.A. Kashcheev (Moscow, Russia)
Amygdalohippocampectomy in Treatment of Epilepsy in Patients with Temporal Lobe Cavernomas

D.N. OKISHEV, O.B. BELOUSHOVA, O.D. SHEKHTMAN, SH.SH. ELIAVA, O.B. SAZONOVA, D.N. KOPACHEV

Burdenko Neurosurgical Institute, Moscow, Russia

Background. In some cases, single-stage or delayed amygdalohippocampectomy (AHE) can be combined with resection of temporal lobe cavernomas for effective treatment of epileptic syndrome. The efficacy of AHE in treatment of temporal epilepsies is proved in general; however, the indications for surgery in patients with cavernomas are not developed. Objective. The study objective was to evaluate the efficacy and safety of AHE in the treatment of epilepsy in patients with temporal lobe cavernomas and to define indications for surgery. Material and methods. Of 14 patients with temporal lobe cavernomas, which manifested as epileptic seizures, 10 patients underwent selective AHE, and 4 patients underwent anteromedial temporal lobectomy. Twelve patients underwent AHE simultaneously with cavernoma resection. Delayed AHE was carried out in 2 cases. All patients underwent preoperative MRI and EEG. Preoperative video-EEG monitoring was performed in 3 cases. The postoperative follow-up was at least 1 year (mean follow-up was 3.3 years). Results. All patients had improvement in the epileptic syndrome. In the postoperative period, 7 patients had no seizures (Engel class IA); of them, 3 patients discontinued anticonvulsants. The surgery outcome depended on the disease duration. Significant postoperative complications in the form of reversible hemiparesis occurred in 1 case. Conclusion. Amygdalohippocampectomy is a highly efficient treatment of severe forms of epilepsy in patients with temporal lobe cavernomas. In the case of a long history of typical temporal seizures and intractable epilepsy, AHE can be performed simultaneously with cavernoma resection.

Keywords: cavernoma, intractable seizures, epilepsy surgery, amygdalohippocampectomy, anteromedial temporal lobectomy.
An analysis of epileptic syndrome involved assessment of seizure patterns, seizure frequency, dynamics, anticonvulsant therapy, and therapy efficacy. The seizure patterns were assessed according to a standard classification: simple focal seizures; focal seizures with a change in consciousness (complicated seizures); seizures with generalization; polymorphic seizures [8, 9]. The seizure frequency was assessed as very rare (1—2 per year or less), rare (3—11 per year), moderate (1—3 per month), frequent (4—14 per month), very frequent (15 or more per month), or acyclic [10]. Seizures were considered as intractable if they persisted upon a successive change of at least two first line antiepileptic drugs administered at a dose not less than a mean therapeutic dose appropriate for age and weight [11].

The presence of “typical” temporal seizures (absences; typical complicated seizures with altered consciousness, often with viscerovegetative reactions, fear, déjà vu/jamais vu states, olfactory and gustatory hallucinations, illusions, derealization, depersonalization, and transition to dialeptic, automotor, or generalized seizure [12]) was observed in all cases. Five patients had generalized tonic-clonic seizures; seizures were very frequent in 2 cases, frequent in 6 cases, moderate in 3 patients, and rare in 3 cases. Ten patients took chronic anticonvulsants. Epileptic seizures in 7 patients met the drug resistance criteria. All these patients suffered from the disease for a long time, at least for 4 years.

When analyzing EEG performed preoperatively in all patients, we allowed for all variants of epileptic or epileptiform activity, its localization and lateralization, and the presence of activity typical of the affected medial structures. A similar epileptiform activity with a typical bilateral localization in the frontal and parietal areas was detected in all cases. The predominance on the ipsilateral side was found in 11 cases. According to the neurophysiologist report, the activity indicating involvement of the medial temporal lobe structures was registered in all cases. A seizure starting on the ipsilateral side was registered during daily video-EEG monitoring in 3 patients.

AHE was performed simultaneously with cavernoma resection in 12 cases. In 2 cases, AHE was conducted 1 year after cavernoma resection due to failure of the first surgery. A total of 9 right-sided and 5 left-sided surgeries were performed. Ten patients underwent selective amygdalohippocampectomy through the lateral fissure (6 right-sided and 4 left-sided surgeries), and 4 patients underwent anteromedial lobectomy (3 right-sided and 1 left-sided surgeries).

The follow-up period in all patients was at least 1 year. The mean follow-up was 3.3 years (from 1 to 5 years). The outcome of epilepsy treatment was evaluated according to the standard Engel scale [13]. Simplified assessment of epilepsy treatment outcomes was performed using the following categories: the absence of seizures after surgery and improvement of the patient’s condition (less frequent seizures or reduced severity of seizures).

We evaluated the outcomes depending on different parameters: gender, age, disease duration, location, seizure frequency and patterns, pharmacoresistance, type of surgery, and completeness of hippocampus resection.

Nonparametric U-test, F-test, and Spearman rank correlation were used for statistical data processing.

**Results**

The main baseline data and surgery results for all patients are shown in Table.

The follow-up data showed that all patients had positive postoperative changes in the course of epileptic syndrome. There were no seizures in 7 patients (Engel class IA). Of these, 3 patients discontinued anticonvulsants (in 1 of 3 these cases, the disease duration was more than 10 years).

Control postoperative CT/MRI scans were available for analysis in 10 patients. The hippocampal body and subhippocampal structures should be resected to the midbrain tectum [14]. Complete resection of the hippocampus foot, substructures of the parahippocampal gyrus, amygdala, and uncus was performed in 8 cases.

Postoperative complications in the form of new clinical symptoms developed in 3 patients. One female patient (#12) who had undergone anteromedial lobectomy complained of a significant loss of recent memory, which, however, did not affect her daily living activities. One patient (#6) experienced moderate postoperative hemiparesis that partially regressed by the time of follow-up evaluation. Another patient (#13) developed homonymous hemianopsia. Thus, the new neurological symptoms developed in 21.4% of cases.

In 1 case (#7), postoperative CT revealed an asymptomatic hematoma in the resected hippocampus bed, which did not require re-operation.

The outcome of epilepsy treatment in our small series depended insignificantly on the disease duration: the mean disease period before surgery was 6.7 years in patients with complete recovery and 12.4 years (p=0.1) in patients who experienced seizures after surgery. Of 7 patients with intractable seizures, complete recovery occurred only in 2 cases. The completeness of hippocampus removal, as well as the other evaluated parameters, did not affect the epilepsy treatment outcome.

Here, we present cases of one-stage and two-stage surgeries.

**Clinical case 1 (one-stage AHE)**

A 19-year-old male patient L.N. (#9) presented with a one year history of polymorphic seizures, with a significant increase in the seizure frequency. By the time of admission to the Neurosurgical Institute, the patient developed generalized tonic-clonic seizures up to 4 times a week and daily absences. By that time, the patient received 800 mg of prolonged carbamazepine per day. The examination findings were as follows: EEG — epileptiform activity in the left temporal area with the signs typical of medial temporal lobe epilepsy; MRI — a typical cavernoma located in the uncus (Fig 1a). On the basis of several factors, a doctor team decided to perform cavernoma resection with simultaneous selective AHE. The patient underwent surgery in 2012. Control MRI revealed that the cavernoma and medial structures were resected (Fig 1b). A single generalized seizure developed 6 months after discharge. So far, there were no recurrent seizures. The patient took anticonvulsants at the same dose. The treatment outcome was interpreted as Engel class 1C, an improvement.

**Clinical case 2 (two-stage surgical treatment)**

A 40-year-old male patient E.I. (#13) presented with a ten year history of polymorphic seizures: complicated partial seizures with automatism and rare seizures with generalization. The typical patient’s seizure was as follows: automotor seizure with dystonia in the left arm and manipulation automatism on the left side; oral chewing automatisms at the beginning of seizure. A generalized seizure was preceded by a turn of the head to the left. The seizure frequency at the time of admission was up to several times per week. Therapy with various drugs...
and their combinations had no effect. On examination: personality and mnestic changes, stiffness, inability to make decisions, and polylogia. MRI revealed a cavernoma of the right mediobasal temporal lobe (Fig. 2a). EEG detected a regional epileptiform activity in the right inferior frontal region and under a right zygomatic electrode. There was a familial history of the disease (the patient’s mother had brain cavernoma).

Surgery I (2013). The cavernoma with adjacent altered brain tissue, including a portion of the hippocampus, was resected (Fig. 2). Follow-up for a year after surgery revealed increased severity of episydrome in the form of an increased seizure frequency (Engel class IV). Video-EEG detected a seizure with a rhythmic epileptiform activity in the right temporal region.

Surgery II (2014). The patient underwent anteromedial temporal lobectomy. A histological biopsy examination revealed focal cortical dysplasia type IIIc. Left homonymous hemianopsia developed after surgery. The patient consulted a neuropsychologist during follow-up: there were no significant changes in memory after surgery. The treatment outcome: rare mild seizures, improvement (Engel class Ib).

Discussion

Treatments of epilepsy associated with hemispheric cavernomas

Treatment of epilepsy associated with a space-occupying lesion by lesion resection (lesionectionomy) is widely used in neurosurgery. In the case of hemispheric cavernomas, simple malformation resection eliminates epileptic seizures in 50—70% of cases and palliates the disease in 60—90% of cases [2, 3]. In order to improve outcomes of epilepsy treatment associated with cavernoma resection, extended surgeries were proposed: resection of a visually altered perifocal zone, ECoG-tailored resection, and cavernomectomy combined with various options of amygdalohippocampectomy.

The idea of lesionectionomy, including the hemosiderin rim, is based on the fact that deposition of blood degradation products contributes to secondary epileptogenesis and neurogenesis [15—17]. In this case, the most functionally altered neurons that directly contact the hemosiderin are removed. In this regard, some authors emphasize the need for resection of the altered gray matter [7]. The reported results of technique application are either statistically insignificant or controversial [18—21]. Our data that are based on the analysis of outcomes of 253 cavernoma resections do not also confirm a significant postoperative improvement of epilepsy after resection of perifocal regions of the altered brain tissue [22]. However, most specialists engaged with this issue believe that the maximally possible resection of the perifocal regions during cavernoma removal is the minimum epilepsy surgery. Many studies also reported improvement in treatment results for ECoG-tailored resection of the epileptogenic zone [6, 23, 24]. It should be noted that this technique is usually used to assess activity of the convexital cortex adjacent to a cavernoma or located in the cavernoma projection. However, the epileptic activity area can be located both deep in a gyrus and at a distance, outside of the area available for electrode placement. Our experience of using intraoperative ECoG in cavernoma

### Characterization of patients, surgical techniques, and outcomes with respect to epilepsy

<table>
<thead>
<tr>
<th>№</th>
<th>Full name</th>
<th>Surgery date</th>
<th>Gender</th>
<th>Age</th>
<th>Disease duration</th>
<th>Side</th>
<th>Pharmacoresistance</th>
<th>Seizure rate</th>
<th>Surgery option</th>
<th>Engel score</th>
<th>Outcome</th>
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<tr>
<td>1</td>
<td>B.F.</td>
<td>2006</td>
<td>F</td>
<td>13</td>
<td>Less than 5 years</td>
<td>d</td>
<td>No</td>
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</tr>
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<td>AHE</td>
<td>IA</td>
<td>Recovery</td>
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</table>
resection did not reveal any influence on the outcome of epilepsy treatment [22].

Making a decision on extended epilepsy surgery is often difficult. This is related to the fact that effective epilepsy surgery requires resection of an additional amount of the brain matter, which is associated with an increased risk for the development of a neurological deficit. For this reason, if there are no factors for an unsatisfactory outcome regarding seizures, many neurosurgeons prefer cavernoma resection and subsequent epilepsy surgery in the case of continuing seizures [25]. However, a number of publications in recent years reported the efficacy of one-stage AHE for seizures associated with temporal cavernomas and the absence of an increased risk of complications compared to conventional malformation resection [7, 26].

Amygdalohippocampectomy is used in the case of severe temporal lobe epilepsy and in the presence of appropriate MRI and clinical and electrophysiological signs, with the clinical symptoms often playing the leading role.

Epilepsy surgery features and auxiliary intraoperative techniques

Amygdalohippocampectomy involves removal of the medial temporal lobe regions affected by secondary epileptization: the hippocampus, amygdala, uncus, parahippocampal gyrus, and some other structures. There is no standard surgical technique. Isolated (selective) amygdalohippocampectomy and anteromedial temporal lobectomy are of crucial importance. The most frequently used surgery options are as follows: anteromedial temporal lobectomy (including resection of the temporal lobe pole) [27], selective amygdalohippocampectomy through the lateral fissure [28, 29], and amygdalohippocampectomy through the middle temporal gyrus (transcortical amygdalohippocampectomy) [14, 30]. The technique efficacy depending on the amount of resection is contradictory. A number of studies [7, 31, 32] demonstrated a higher efficacy of the most radical surgery, anteromedial temporal lobectomy. Some authors [29, 33—35] claimed that the efficacy of selective amygdalohippocampectomy in epilepsy treatment was equivalent to that of lobectomy. Furthermore, hippocampal transection was reported to be sufficient for satisfactory seizure control [36]. The data on possible adverse consequences of a certain technique regarding the neuropsychological patient status are also ambiguous [32, 34]. Given the different points of view on this issue, each surgeon chooses a technique based on his own experience and clinic experience. Previously, selective amygdalohippocampectomy was mostly used at the Neurosurgical Institute. Currently, anteromedial temporal lobectomy with resection, up to 3—4 cm, of the anterior middle and inferior temporal gyri, amygdala, and hippocampus (posteriorly, up to the midbrain tectum) is preferably used for medial temporal lobe epilepsy, regardless of the seizure etiology. This approach was chosen based on the available data on a better efficacy of this surgery option compared to selective AHE and ease of resecting the medial temporal structures through the formed window, with the ability to avoid excessive traction on the frontal lobe upon access. It is worth mentioning that a number of authors [27] recommend to preserve the superior temporal gyrus during anteromedial temporal lobectomy.

ECoG is widely used as an intraoperative auxiliary method. This is the only method enabling intraoperative assessment of the cerebral cortex activity. This method has some limitations: recording is short-term and often does not reveal typical changes (low sensitivity, complexity of data interpretation). In our series, ECoG was performed in 5 cases. In this case, it influenced the operative plan in 1 (#1) case: an activity of the neocortical temporal lobe regions was detected, which resulted in their subsequent resection (the resection had not been planned before recording). Intraoperative recording of scalp EEG with assessment of dynamic changes is also possible in the presence of persistent interictal epileptic activity. “Normalization” of scalp EEG during surgery was recorded in patient #2.

In 2 cases in our series (#12 and #13), anteromedial lobectomy was performed during the second stage — more than a year after cavernoma resection, due to surgery failure. Extended surgery might have been initially planned in both patients due to pharmacoresistance and a long disease history. But in some cases, the concept of a second surgical stage is justified in epilepsy treatment. The authors [25] adhering this approach substantiated it by the following reasons: 1) simple

Figure 1. A patient L.N. (#9).

a — a preoperative T2-weighted MRI scan; b — an intraoperative view of the hippocampus and choroidal fissure through the left transsylvian approach; c — a control T2-weighted MRI scan (see the explanation in the text).
Cavernomectomy proved to be a safe and very effective technique for treatment of epilepsy associated with the presence of cerebral cavernomas, even in the case of severe intractable seizures; 2) a positive effect of ECoG and resection of extra brain tissue was confirmed in some studies, with the difference being minimal; 3) brain tissue resection can potentially lead to the development of a neurological deficit; 4) long-lasting examination and involvement of an additional intraoperative technique and specialists lead to a substantial increase in the overall duration of hospital stay and treatment costs. However, it should be noted that re-operation is often technically more complex, and, in some cases, it is very advisable during primary examination of the patient.

Complications of epilepsy surgeries

Amygdalohippocampectomy belongs to surgeries with an increased risk of complications. Complications in the form of a persistent disabling neurological defect usually develop in single cases, and the likelihood of their development largely depends on surgeon experience. There is a risk of hemorrhagic and ischemic complications associated with injury to blood vessels and small perforating branches as well as complications caused by direct damage to certain brain structures: visual field defects due to Meyer loop damage as well as impairments of memory, behavior, and emotional reactions due to interventions on the amygdalohippocampal complex. The development of hemianopsia (case #2) is a quite typical feature. A high risk for developing a visual defect was shown to be associated with anteromedial temporal lobectomy [37, 38]. Disorders of higher cortical functions detected during specific neuropsychological studies were found in many trials and most often manifested in the form of memory impairments, predominantly of the oral-aural modality [34, 39, 40]. A defect can manifest postoperatively, both in the dominant hemisphere and in the subdominant hemisphere. The defect severity is usually more pronounced after left-sided AHE. Some authors indicate that the symptom complex of these disorders is often more complicated and also involves various emotional disturbances, up to severe depressions [41]. Assessment of postoperative psycho-emotional disorders should include the preoperative features of patients whose psycho-emotional status is often initially altered due to a long history of epileptic seizures. A number of studies [29, 42] showed a smaller number of complications associated with selective AHE; other authors [32] argued the reliability of these findings. In our series, memory disorders occurred in a female patient after anteromedial lobectomy.

The role of various factors in outcome of epilepsy surgery

The dependence of good treatment outcome on several factors was analyzed in a series of studies. Reliable predictors of a good outcome include a short history of seizures (up to 1—2 years according to different authors) and effective anticonvulsant therapy [3, 21, 25, 43]. Accordingly, poor treatment outcomes are more frequently observed in patients with a long history of the disease, large number of seizures in the medical history, and intractable seizures. There are no reliable data on a greater...
efficacy of a certain surgery option for cavernomas. In our series, the outcome was also independent of the completeness of hippocampus removal. However, the surgeon should always adhere to the chosen technique as much as possible.

Conclusion

Good and excellent results in all patients of our series confirm a high efficacy of AHE in the treatment of epilepsy in patients with temporal lobe cavernomas. In our opinion, AHE is recommended for this pathology in the presence of the following factors: typical temporal lobe epilepsy with a disease history of more than two years and with frequent or very frequent intractable seizures. In these cases, AHE should be carried out simultaneously with cavernoma resection. In other cases, a decision on the AHE advisability should be based on preoperative and intraoperative electrophysiological data, in addition to clinical data, in order to identify and localize the source of epileptic activity. If AHE is not advisable, cavernoma removal with complete resection of macroscopically changed brain tissue is recommended to eliminate blood degradation products and ensure a certain degree of disconnection of potential pathological pathways of rhythmic excitation. AHE can be performed in the late periods after cavernoma resection if there is no antiepileptic effect of cavernoma and surrounding brain tissue resection.

Authors declare no conflict of interest.

REFERENCES


Commentary

Treatment of epilepsy both in adults and in children is a complicated task. In cases of symptomatic epilepsy caused by structural brain defects, removal of the surgical epileptogenic substrate based on adequate presurgical examination and selection of an optimal surgical tactics yields good results. This relieves the patient from seizures and the need for long-term use of antiepileptic drugs. However, it should be taken into account that resection of an affected anatomical substrate alone is insufficient for complete recovery of the patient from epilepsy in many cases. In this regard, presurgical neurophysiological examination of patients and intraoperative electrocorticography are of great importance. It should be noted that the need for additional examination to determine the indications for epilepsy surgery and the advisability of extending the amount of resection through involvement of the epileptogenic structures are often ignored by neurosurgeons dealing with neuro-oncology and vascular neurosurgery.

The work is prepared in accordance with the classical scheme and contains a table and two illustrations. The article reviews the relevant literature data, clearly presents the authors’ view of the problem, and analyzes the treatment outcomes in a small series of 14 patients. It is important that all patients were followed-up. Two clinical cases are presented, one of which demonstrates simultaneous resection of a cavernoma and the hippocampus, and the second describes two-stage surgery. The study clearly demonstrates that the technique is efficient but associated with a risk of complications. In this regard, the indications for one-stage resection of cavernoma and medial temporal lobe structures should be considered carefully.

The article is useful for neurosurgeons and neurologists/epileptologists as well as for a wide range of medical specialists.

A.A. Kholin (Moscow, Russia)
Trigeminal Neuralgia and Hemifacial Spasm Associated with Vertebrobasilar Artery Tortuosity

YU.A. GRIGORYAN, A.R. SITNIKOV, G.YU. GRIGORYAN

Federal Center of Medicine and Rehabilitation of the Ministry of Health of the Russian Federation, Moscow, Russia

Tortuous vertebrobasilar artery (TVBA) often causes neurovascular conflicts in patients with trigeminal neuralgia (TN) and hemifacial spasm (HFS). Microvascular decompression (MVD) in these circumstances is hindered by stiffness of the enlarged and dilated artery and often results in poor outcomes. The surgical strategy in cases of trigeminal neuralgia and hemifacial spasm caused by the TVBA should be refined in order to achieve good outcomes. **Material and methods.** MVD was performed in 268 TN patients and 71 HFS patients. TVBA as a compressing vessel was detected in 30 cases (11 cases of TN, 18 cases of HFS, and 1 patient with painful tic convulsivii). All patients underwent MVD and retrospective analysis of clinical outcomes. **Results.** Compression caused by the vertebral artery was found in all HFS patients and 4 TN patients, and compression caused by the basilar artery was observed in 7 TN cases. Additional compression of the cranial nerve root entry/exit zone by cerebellar vessels was observed in 21 cases. TVBA was mobilized by dissection of arachnoid adhesions between the vessel and the brainstem and retracted laterally. Then, TVBA was retracted from the brainstem in the caudorostral direction. These manipulations resulted in “spontaneous” decompression of the cranial nerves without placing prostheses between the artery and nerve root entry/exit zone. In all cases (except two), the displaced TVBA was fixed between the enlarged artery and brainstem using pieces of patient’s muscle and adipose tissues followed by application of fibrin glue. In 1 case, cylindrical silicone prosthesis was used. In another case, TVBA was retracted using a fascial loop fixed to the dura mater of the petrous pyramidal by means of a suture. After MVD, TN and HFS symptoms completely regression. There were several transient complications and 2 cases of permanent hearing deficiency. No recurrence of clinical symptom was observed. **Conclusion.** MVD is the most effective surgical treatment of TN and HFS caused by TVBA. TVBA should be retracted from the brainstem without placing prostheses at the nerve root entry/exit zone.

**Keywords:** trigeminal neuralgia, hemifacial spasm, tortuous vertebrobasilar artery, microvascular decompression.

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Abbreviations:

BA — basilar artery  
SCA — superior cerebellar artery  
HFS — hemifacial spasm  
PICA — posterior inferior cerebellar artery  
TVBA — tortuous vertebrobasilar artery  
CT — computed tomography  
MVD — microvascular decompression  
MRI — magnetic resonance imaging  
VA — vertebral artery  
AICA — anterior inferior cerebellar artery  
TN — trigeminal neuralgia  
CN — cranial nerves

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Trigeminal neuralgia and hemifacial spasm result from compression of the corresponding cranial nerve roots caused not only by cerebellar arteries, but also major blood vessels, such as vertebral and basilar artery. In the case of hemifacial spasm, compression of the facial nerve fibers by the vertebral artery is relatively more common, while trigeminal neuralgia resulting from the compression of the trigeminal nerve root by the tortuous basilar artery is represented by a small number of cases [1—9].

There are several different terms for significant dilation, elongation, and tortuosity of the intracranial arteries: fusiform (spindle-shaped) aneurysms, giant intracranial fusiform aneurysms, atherosclerotic aneurysms, ectasia of intracranial arteries, and megadolichoectasia. These deviations are detected in both carotid and vertebrobasilar brain systems, but characteristic changes are most often observed in large posterior circulation arteries. Dilation and elongation of the vertebral and basilar arteries with significant tortuosity is usually called megadolichovertebrobasilar anomaly, dolichoectasia of the vertebrobasilar artery, and vertebrobasilar dolichoectasia. Elongation and tortuosity of the arteries is not always accompanied by their significant dilation and in most publications this anomaly is referred to as tortuous vertebrobasilar artery (TVBA). TVBA has various clinical manifestations and in rare cases can manifest as intracranial hemorrhage and obstructive hydrocephalus, but usually it causes ischemic strokes, which occur as a result of decreased blood flow and parietal thrombosis in the abnormally tortuous vessels and their thin branches. Other clinical symptoms (spastic tetraparesis, trigeminal neuralgia, hemifacial spasm, vagoglossopharyngeal neuralgia) are caused by direct...
compression of both the brainstem and cranial nerve roots by rigid dilated arteries [10—12].

In the case of neural structure compression caused by TVBA, complete decompression of the cranial nerve roots is very complicated due to dense atherosclerotic walls of a compressing vessel and therefore neurovascular decompression is accompanied by a large number of complications and poor results. Various modifications of the surgical technique of vascular decompression are used in the case of compression of neural structures with large tortuous vessels, including a wide range of surgical techniques, from placement of metal implants between the nerve root and the rigid vessel to adhesive fixation of the displaced vertebrobasilar artery [1—9, 13—48].

In this paper, we present our own experience of vascular decompression in patients with trigeminal neuralgia and hemifacial spasm caused by nerve root compression by TVBA.

Material and methods

Microsurgical exploration of the cerebellopontine angle was carried out in 339 patients with trigeminal neuralgia (268 cases) and hemifacial spasm (71) with vascular compression of the corresponding cranial nerve roots during the period from 1987 to 2015. However, this paper includes 30 cases, where the compression of the parastem segments of the trigeminal and facial nerve root was caused by TVBA (see Table). Among them, 11 patients suffered from trigeminal neuralgia (2 females and 9 males aged 48 to 65 years) and 18 had hemifacial spasm (13 females and 5 males aged 40 to 68 years). In one case, there was unilateral combination of trigeminal neuralgia and hemifacial spasm (painful tic convulsif) in a 77-year-old female.

All patients underwent computed X-ray and/or magnetic resonance imaging (CT, MRI) to visualize the vascular and neural structures, evaluate the neurovascular relationships and the degree of deformation of nerve roots and brainstem.

Surgical approach to the parastem segments of the trigeminal and facial nerve roots was carried out through the retromastoid craniotomy. The approach to the trigeminal entry zone was carried out by means of the caudomedial displacement of the superolateral portions of the cerebellar hemisphere, while the exit zone of the facial nerve from the brainstem was visualized using the superomedial retraction of the inferolateral portions of the cerebellar hemisphere. After dissecting the arachnoid and its adhesions, trigeminal and facial nerve roots were examined starting from the brainstem throughout their cisternal segments. Vascular decompression was achieved by mobilization and displacement of the compressing vessel away from the entry/exit zones of the nerve roots accompanied by placement of implants between the TVBA and brainstem.

After surgery, all patients underwent brain CT scan in order to rule out intracranial complications, 14 patients underwent MRI to assess new neurovascular relationships. Surgical treatment results were evaluated based on two criteria: in the case of the complete disappearance of clinical presentation of the disease, surgical outcome was considered as “excellent”, while in cases where pain or involuntary contractions of the facial muscles of any degree, frequency, and intensity persisted, outcome was considered as “poor”.

Results

Trigeminal neuralgia was characterized by typical paroxysmal pain with trigger zones and responded to treatment with carbamazepine, whose efficacy gradually decreased over time. Neuralgia was located on the right in 3 patients, and on the left in 8 patients. In 6 cases, pain syndrome covered the second and third branches, in 3 cases — the first and second branches, in 1 case — the second branch, and in another 1 case — the third branch of the trigeminal nerve. The duration of the disease prior to the surgery ranged from 6 months to 7 years. Three patients underwent alcoholization of the peripheral branches of the trigeminal nerve (see case No 2 in the Table), hydrothermal destruction of the root (see case No 3), and stereotactic radiosurgery using GammaKnife (see case No 10) with a short-term (2—4 months) pain relief. Preoperative neurological examination of 5 patients (see cases No 2, 3, 4, 7, 8 in the Table) showed sensory disorders on the impaired side of the face in the form of mild hypoesthesia without signs of involvement of other cranial nerves. In one case (see case No 1 in the Table), the preoperative stage revealed contralateral facial paralysis, which spontaneously occurred within 1 year after manifestation of trigeminal neuralgia.

In all patients, hemifacial spasm was tonic-clonic with Marcus Gunn phenomena: it was steadily progressing and gradually involved the entire facial musculature. Furthermore, all patients demonstrated almost no response to years-long drug therapy. Duration of the disease prior to the vascular decompression was 3—15 years. In 7 patients with hemifacial spasm, there were pronounced right sided involuntary contractions of facial muscles, and the remaining 11 patients had left-sided deficit. In all cases, involuntary contractions began with twitching of the orbicular muscle of the eye and gradually spread to the rest of facial muscles. Since drug therapy (anticonvulsants, antipsychotics, vitamins) was ineffective, 4 females underwent Botulinum therapy, which resulted in a short (2 to 5 months) effect. By the time of surgery, 2 of them retained paresis of some groups of muscles, which were injected with Dysport. However, the severity and frequency of involuntary contractions of the other facial muscles remained unchanged. Hearing deficiency on the side of hemifacial spasm and dysfunction of other cranial nerves was not observed. In one case (see case No 13 in the table), there was concomitant contralateral trigeminal neuralgia, which was subsequently eliminated by percutaneous radiofrequency trigeminal rhizotomy.

The only case of painful tic convulsif reported in our previous publication was characterized by successive emergence of unilateral trigeminal neuralgia and hemifacial spasm with a several-year-long interval [22].

CT and MRI showed characteristic signs of TVBA, such as dilation, elongation, and tortuosity of the vertebral and basilar arteries. In all cases, there was a pronounced lateral displacement of the vertebrobasilar artery loop with location of the vessel in the cerebellopontine angle. In the present group of patients, the lateral convexity of the vertebrobasilar artery loop matched the side of cranial nerve injury (Fig. 1).

According to the MRI, in patients with trigeminal neuralgia, compression of the trigeminal entry zone was caused by the loops of the basilar artery in 7 cases and vertebral artery in 4 cases. In the case of hemifacial spasm, compression of the exit zone of the facial nerve was always caused by the vertebral artery loop. TVBA caused significant deformation of the medulla oblongata or pons, which sometimes hindered visualization of nerve roots due to significant displacement and angulation of its fibers caused by a large diameter vessel (Fig. 2).

Microsurgical exploration detected TVBA with thick yellow walls and multiple vasa vasorum. The loop of the dilated
artery deformed the pons and was located in the trigeminal entry zone, displacing the fibers of trigeminal nerve root upwards and backwards. In 9 patients, the initial segments of the superior or anterior inferior cerebellar artery were also observed in the trigeminal entry zone and the entrances of the cerebellar arteries were usually covered by the trigeminal nerve root (Fig. 3a). Compression of the exit zone of the facial nerve was in all cases caused by the vertebral artery loop (Fig. 4a). In 2 cases, one of which was described above, compression of the facial nerve fibers was caused by the loop of the contralateral vertebral artery located posterior to the ipsilateral vessel [23]. In 13 cases, the compression of the parastem portion of the facial nerve was additionally caused by the initial segments of the anterior and posterior inferior cerebellar arteries; the vertebral artery and the entrances of the cerebellar arteries were located immediately under the exit zone of the facial nerve. In the case of painful tic convulsif, both nerve roots were compressed by the contralateral vertebral artery [22].

Vascular decompression of cranial nerves was carried out by the arachnoid dissection and transposition of the arterial vessel away from the nerve roots. TVBA was carefully shifted laterally from the nerve root to assess its mobility and visualize thin perforating vessels to the brainstem (see Fig. 3b and Fig. 4b). Displacement of the large artery was in some cases limited by the length of perforating branches to the brainstem. For this reason, special attention was paid to prevent stretching and bending of these thin arteries, since their injury may result in ischemic injury of stem structures.

The dissection of arachnoid adhesions fixing the major artery to the brainstem enables additional displacement of the vessel and nerve root decompression. The need for separation and clear visualization and the TVBA located caudal to the nerve root is an important methodological aspect of vascular decompression. In the case of the neurovascular conflict caused by major blood vessel, decompression in the “bottom-up” direction enables TVBA transposition without manipulation on the nerve root, resulting in minimization of possible dysfunction of the corresponding cranial nerve. In the case of additional compression of the cranial nerve caused by the initial segments of the cerebellar arteries, even without significant distorting impact on the entry/exit radicular zones caused by the nearby TVBA, the use of the “bottom-up” decompression surgical technique also leads to elimination of neurovascular conflict. Gradual lateral transposition of the large vessel is accompanied by spontaneous retraction of the cerebellar arteries originating at TVBA from the parastem portions of cranial nerves.

### Clinical data of patients with trigeminal neuralgia and hemifacial spasm caused by tortuous vertebrobasilar artery

<table>
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Implants are placed in the fissured space formed between the laterally displaced TVBA and brainstem. Implants, which vary in their size and number, are also placed in the caudorostral direction with gradual evaluation of the strength of artery fixation and the need to insert additional more rostral implant. Autologous or synthetic implants located between vessel walls and the brainstem below the entry/exit zones of the cranial nerves fix the new position of the displaced artery and have no direct contacts with the fibers of the nerve roots. In most cases, we used fragments of muscle and adipose tissue (see Fig. 3c, and Fig. 4c), and in one case we applied cylindrical porous silicon protector, which was placed onto the trigeminal nerve root. After elimination of the neurovascular conflict, displaced TVBA was additionally fixed with several drops of fibrin glue in order to prevent displacement of the installed implants (see Fig. 4d).

In one case, TVBA displaced in the lateral and inferior direction from the trigeminal nerve root was fixed using fascial loop. Fascial strip was placed around the artery and sewed on to the dura mater of the petrous pyramid with interrupted suture (Fig. 5).

Implementation of this technique is possible only when there is sufficient “free working space” between the distal segments of the cranial nerve roots at their exit to the corresponding bone-dural channels.

One patient with trigeminal neuralgia additionally underwent partial trigeminal rhizotomy. Trigeminal entry zone and the adjacent portions of the pons were severely compressed by a giant TVBA loop. Due to the tight adherence of the artery to the petrous pyramid, only minimal retraction of the former was possible, which did not provide complete decompression of neural structures. After installation of autoimplants, inferior portions of the stretched and deformed root of the trigeminal nerve were dissected in order to eliminate neurological syndrome.

There were no lethal outcomes or infectious complications after surgery. In 2 patients, there was liquorrhea, which was eliminated using short-term (3—5 days) external lumbar drainage. In all cases, the immediate postoperative period was characterized by complete regression of pain syndrome in patients with trigeminal neuralgia and involuntary contractions of facial muscles associated with hemifacial spasm. Subsequent follow-up (1 to 15 years) showed stable elimination of facial pain and hyperkinesis and no recurrence of the disease.

The symptoms of injury of cranial nerves located at surgical area and deterioration of the functions of nerve roots subjected to vascular decompression were considered as complications of the surgery. In the group of patients with trigeminal neuralgia, abducens paresis developed in one patient and regressed within 1 month after surgery. Emergence and/or augmentation of facial hypoesthesia was observed in 2 cases and the severity of sensory failure also decreased within 4—5 weeks. Ipsilateral permanent hearing deficit was observed in 2 patients with hemifacial spasm. In one patient with intact hearing, paresis of the facial nerve developed two days after surgery and regressed within a few weeks.

Postoperative MRI showed that pre-existing neurovascular conflict disappeared and the absence of vascular structures at the entry/exit zone of the corresponding nerve root was the most demonstrative sing (Fig. 6).

### Discussion

IVBA is a rare cause of trigeminal neuralgia and it is observed in 2.8—7.7% of patients with vascular compression [3, 5, 9, 46, 47]. Involvement of TVBA in the neurovascular conflict is more common in patients with hemifacial spasm, reaching 14% [1, 2, 6, 7, 26].

W. Dandy [49] was the first who detected compression of the parastem segments of the trigeminal nerve root caused by thickened vertebrobasilar artery in patients with trigeminal neuralgia. The author used the term “cirroid (S-shaped) aneurysms”, putting emphasis on the elongation, tortuosity, and dilation of the artery with dense walls, in order to specify characteristic changes in the shape and dimensions of the vessel. E. Campbell and C. Keedy [50] and W. Gardner and G. Sava [51] detected compression of the brainstem exit zone.
of the facial nerve caused by adjacent loops of the tortuous and dilated vertebrobasilar artery.

Linskey et al. [3] compared demographic and clinical characteristics of patients with trigeminal neuralgia caused by compression by cerebellar arteries and TVBA. The group of patients with vertebrobasilar artery compression was older and characterized by predominance of male patients. They found predominant involvement of the left side of the face, as well as high correlation with ipsilateral hemifacial spasm and hypertension. According to J. Kim et al. [26], hemifacial spasm caused by compression with TVBA was observed mainly on the left side and was 3.5 times less common in male patients. Higher incidence of left-sided injury can be explained by asymmetric diameter of vertebral arteries with higher caliber of ipsilateral vessel. Another important factor is more pronounced pulse wave transmission due to the branching of the left vertebral artery from the subclavian artery originating directly from the aortic arch, as opposed to the right vertebral artery originating from the brachiocephalic trunk. Combination of these hemodynamic factors results in tortuosity and dolichoectatic changes in the distal (intracranial) segments of the left vertebral artery and the whole vertebrobasilar artery [10, 11].

According to M. Linskey et al. [3], in 31 (2.2%) of 1404 patients with trigeminal neuralgia who were operated on by P. Jannetta, isolated compression of trigeminal entry zone caused by the vertebrobasilar artery was detected in 26% of cases. Nerve fibers were compressed by the vertebral artery in 18 (58%) cases, basilar artery — in 12 (39%) cases, and vertebrobasilar junction — in 1 (3%) cases. The remaining patients had compression caused by several vessels, and the most common intraoperative pattern of the neurovascular conflict was represented by the rostral displacement of the trigeminal nerve root caused by TVBA located below and its compression from above by the superior cerebellar artery or venous vessel. Among the 10 patients with trigeminal neuralgia caused by vertebrobasilar dolichoectasia, N. El-Ghandour [18] have found nerve root compression by only TVBA in 6 patients, while in other cases neurovascular conflict further involved cerebellar arteries and veins. X.-S. Yang et al. reported 10 cases [47], including 2 cases with compression of the trigeminal nerve root caused by the vertebral artery, 3 cases — by the vertebral and cerebellar artery, 1 case — by the vertebral artery and vein, and 4 cases — by the basilar and cerebellar arteries.

In the clinical material reported by M. Linskey et al. [3], mild hypoesthesia was observed in 51.6% of patients, which was caused by previous surgery in 9 patients. However, 7 patients who did not previously underwent surgical procedures also had sensory impairments. Spontaneous sensory disorders detected in our group of patients are indicative of the severity of
In 232 (14%) of 1663 patients with hemifacial spasm who were operated on by T. Fukushima, compression of the exit zone of the facial nerve was caused by tortuous vertebral artery, and in 123 (53%) of them neurovascular conflict further involved cerebellar artery [2]. Among the 143 cases reported by M. Samii et al. [7], facial nerve compression by the vertebral artery was observed in 32 (26.6%) cases, where isolated involvement of the vertebral artery was observed only in 6 patients, while in the rest of cases, both anterior and posterior inferior cerebellar arteries were located at the nerve root exit zone. S. Nagahiro et al. [6] have found compression of the facial nerve by the vertebral artery in 14 of 68 operated patients with hemifacial spasm, but in 11 of them nerve root was further compressed by the cerebellar artery.

Increased incidence of postoperative neurological disorders of the cranial nerves is caused by numerous surgical procedures for mobilization and transposition of the major arteries. Displacement of major vessels is accompanied by action of both surgical instruments and dense arterial structures, changing relationships with adjacent nerve structures, on the surrounding cranial nerves (trochlear nerve, abducent nerve, acoustical nerve, glossopharyngeal nerve, and vagus nerve). In the postoperative period, M. Linskey et al. [3] observed emergence or strengthening of facial hypoesthesia in 13 (41.9%) of 31 patients with trigeminal neuralgia, transient double vision due to the weakness of the trochlear and accessory nerves was observed in 22.6%, and hearing impairment was observed in 12.9% of patients. N. El-Ghandour [18] reported transient sensory disturbances on the face in 2 patients, trochlear nerve paresis in 1 patient, and weakness of the facial muscles in another 1 out of 10 patients in the group, while X.-S. Yang et al. [47] reported postoperative complications such as facial numbness only in 1 case out of 10. In a series of 45 observations [5], T. Fukushima described similar findings: postoperative trigeminal hypoesthesia in 29% of cases, diplopia in 24% of cases, facial paresis in 7% of cases, and hearing loss in 4% of cases. The above results indicate that compression of the trigeminal nerve root by major artery can result in development of various neurological consequences of neurovascular decompression.

Hearing impairment, weakness of the facial muscles, caudal nerve paresis, and ischemic strokes of the medulla oblongata in the postoperative period, M. Linskey et al. [3] observed emergence or strengthening of facial hypoesthesia in 13 (41.9%) of 31 patients with trigeminal neuralgia, transient double vision due to the weakness of the trochlear and accessory nerves was observed in 22.6%, and hearing impairment was observed in 12.9% of patients. N. El-Ghandour [18] reported transient sensory disturbances on the face in 2 patients, trochlear nerve paresis in 1 patients, and weakness of the facial muscles in another 1 out of 10 patients in the group, while X.-S. Yang et al. [47] reported postoperative complications such as facial numbness only in 1 case out of 10. In a series of 45 observations [5], T. Fukushima described similar findings: postoperative trigeminal hypoesthesia in 29% of cases, diplopia in 24% of cases, facial paresis in 7% of cases, and hearing loss in 4% of cases. The above results indicate that compression of the trigeminal nerve root by major artery can result in development of various neurological consequences of neurovascular decompression.

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of transient and permanent cranial nerve dysfunction (facial, auditory, and caudal group) in the case of compression by TVBA was not significantly different from the number of neurological complications in the case of compression by the cerebellar arteries.

In most cases, facial neuralgia disappears after neurovascular decompression. However, according to M. Linskey et al. [3], in 3 of 31 patients, pain relapsed 1, 3, and 5 years after the surgery. S. Miyazaki et al. [5] reported 2 cases of relapsed trigeminal neuralgia among 45 patients 2 and 3 months after the surgery. Similar results were observed during treatment of hemifacial spasm caused by TVBA, where success rate in the long-term follow-up was close to 90%, which is similar to that in patients with facial nerve compression caused by the cerebellar artery [6, 26].

Teflon implants, whose number and size can be easily modeled depending on the particular surgical findings, are typically used to eliminate the compression of the entry/exit zones of the cranial nerve roots caused by TVBA. Thus, M. Linskey et al. [3] used Teflon implants in 22 cases, ivalon — 3, and silicone — 1 for neurovascular decompression of the trigeminal nerve root. They also used pieces of muscle tissue in 2 patients and straight fenestrated aneurismal clip in 1 case. In 2 cases, basilar artery could not be safely displaced from the trigeminal nerve root due to its extremely high density and rigidity. In one of these cases, total sensory rhizotomy was carried out and in the second case, the partial intersection of the sensitive portion was completed by decompression of the remaining portion of the root by the muscle implant [3].

The main goal of the vascular decompression of cranial nerves is to eliminate the pulsating effects of the vessels located at the entry/exit zones of the nerve. Microsurgical interposition technique is used in the everyday practice, when several small synthetic implants, typically in the form of lumps made of Teflon wool, are gradually placed between the nerve root and adjacent vessel. This technique has been successfully used not only in cases of compression caused by the cerebellar artery with relatively small diameter, but also in patients with compression of cranial nerves caused by major vessels, such as TVBA. However, the use of interposition technique to eliminate neurovascular conflict caused by major arterial vessels has certain limitations. Along with well-known complications, such as displacement of installed implant and development of inflammatory granulomas in the postoperative period, the specific feature of the method is the need to insert significantly larger than usual amount of implanted material between the spine and dolichoectatic artery. This neurovascular decompression technique results in displacement and deformation of the nerve root itself, rather than retraction of the major artery away from the original position, due to high density of its walls and high intravascular pressure. Interposition technique is associated with high efficacy of elimination of trigeminal neuralgia despite the high incidence of sensory disturbances on the face (the effect of partial rhizotomy), but it cannot be used in the case of hemifacial spasm due to almost inevitable postoperative paresis of the facial nerve and hearing impairment.

There are various uses of isolation techniques in combination with interposition technique to eliminate compression of cranial nerve roots caused by TVBA. Isolation method includes wrapping the nerve roots and/or compressing vessels with various implant in the form of strips and bands, as well as installation of cylindrical and fenestrated aneurysmal clips separating vascular and nerve structures from each other. However, this surgical technique is not fundamentally different from the interposition technique, since inserted implants are in contact with the nerve roots, and requires much larger number of manipulations. Extreme variants of this kind of surgical “redundancy” are shown in 2 cases of trigeminal neuralgia, where titanium implants designed for fixation of bone flaps are used to isolate TVBA from the trigeminal nerve root [14, 44].

Transposition of the vessels involved in the neurovascular conflict with minimal surgical impact on neural structures is the most effective method of vascular decompression of the cranial

Figure 5. Intraoperative photograph of trigeminal neuralgia
Fixation of the displaced vertebral artery with fascial loop.
a — left trigeminal nerve root is displaced upward and backward by the vertebral artery loop; b — vertebral artery is displaced in downward and lateral direction and fixed with a fascial loop (FL) to the dura mater of the petrous pyramid.
nerve roots. After identifying compressing blood vessels in the entry/exit zones of the corresponding nerve roots, surgical actions are aimed at mobilization and displacement of the arteries and fixation of new position of vascular structures is the final stage of neurovascular decompression. Due to severe tortuosity and high density of atherosclerotic walls, displacement of major vessels away from the nerve roots is a complicated operation. Dissection of arachnoid adhesions, fixing TVBA to the brainstem, should begin below the level of the compressed nerve root. In the present series of observations, in patients with trigeminal neuralgia, we started arachnoid dissection at the level of the internal auditory canal and related nerve complex, and in patients with hemifacial spasm, we started with separation of the caudal group of nerves. For decompression of the trigeminal nerve root, it is always recommended to start mobilization of the vertebrobasilar artery at the level of the caudal group of nerves [9, 25, 47]. This method of phased “bottom-up” arachnoid dissection along the brainstem enables gradual mobilization of TVBA, assessment of its mobility, and timely identification of the entrances of cerebellar and brainstem arteries covered by nerve roots.

Placement of implants between the brainstem and the vessel is the most technically simple method of TVBA fixation in the new spatial position. Most authors use numerous teflon implants in the form of pellets and lumps to tampon the space formed after the transposition, which provides reliable fixation of the newly created neurovascular relationships. There are various methods of fixation of transposed artery using adhesive compositions, “suspending loops” made of synthetic materials, dural and fascial flaps, surgical sutures passed around or through the vascular adventitia, as well as fenestrated aneurysmal clips [8, 13, 15, 19, 21, 24, 28—43, 45—48]. The use of loop fixation of the artery is the most reasonable way of neurovascular decompression, since it eliminates the need to install large implant and reduces the chance of developing aseptic granuloma. However, implementation of this technique requires expansion of the surgical field by increasing cerebellum retraction and may be accompanied by additional injury of both nervous and vascular structures with increased number of postoperative complications. In most cases, we used the pieces of muscle and adipose tissue, which were inserted in a phased manner for fixation of displaced artery away from the brainstem. Placement of autoimplants is easy to do because of the possibility of arbitrary modeling of the size of tissue pieces and requires no additional surgical procedures after mobilization of the vessel. During implant placement in the “bottom-up” direction and gradual TVBA retraction from the brainstem, displaced vessel “spontaneously” moves away from the entry/exit zone of the compressed cranial nerve. Due to “spontaneous” decompression, surgical manipulation on the nerve roots are not performed and implants are not installed between the TVBA and cranial nerves, which prevents the development of postsurgical cicatricial deformity of nerve fibers. Newly created neurovascular relationships are further strengthened with fibrin glue, which preserves the spatial arrangement of the displaced vessel until the final fixation of TVBA by cicatricial adhesions with the autoimplant and dura mater.

Conclusions

1. Mobilization and displacement of the TVBA is performed through arachnoid dissection in the “bottom-up” direction, which minimizes surgical manipulations on cranial nerve roots.
2. The implants are placed between the displaced large artery and the brainstem, rather than nerve root.

3. Preservation of intact entry/exit zones of cranial nerves reduces the likelihood of relapses, resulting from cicatricial deformities of the nerve roots.

4. The use of these surgical techniques results in high effectiveness of microvascular decompression in patients with trigeminal neuralgia and hemifacial spasm caused by TVBA.

Authors declare no conflict of interest.


**Commentary**

Trigeminal neuralgia (TN) and hemifacial spasm (HFS) are manifestations of the hyperfunction of intracranial nerves, which are mainly caused by vascular compression of their parastem portions at the cerebellopontine angle. TN, where the superior cerebellar artery is the main compressing vessel, is more common compared to HFS caused mainly by the compression caused by the anterior inferior cerebellar artery. Vascular decompression of the cranial nerves is a well developed operation, which is increasingly more widely used in Russian neurosurgery, aimed at elimination of the causes of cranial nerve hyperfunction. During this operation, complications may occur only in the case of rare forms of operational topographic anatomy of the cerebellopontine angle. These rare forms include the cases of compression of the trigeminal and facial nerves caused by the vertebral artery (VA) or the basilar artery (BA). In this regard, the relevance of this article is undoubted, and it will be interesting primarily to those neurosurgeons who use the surgery of cranial nerve vascular decompression in their everyday practice.

The authors have extensive experience in vascular decompression surgery of the cranial nerves, which is also evidenced by a large number of patients (30) with either VA or BA as a main compression agent. All patients underwent clinical examination and the results were used to establish appropriate diagnosis, either TN or HFS. Furthermore, all patients underwent neurovisualization examinations, including computed tomography and magnetic resonance imaging (MRI). The authors state that these studies are especially valuable to diagnose the hyperfunction of the cranial nerves, and for this reason, I would like to emphasize once again that the diagnosis of TN or HFS can be established solely based on the clinical manifestations of the disease. The objective of neuroimaging is not so much confirmation of vascular compression of cranial nerves by some vessel as the detection of space-occupying lesions, aneurysms in the cerebellopontine angle, vascular malformations, demielinisation foci in the brainstem, which in a few percent of the cases are the cause of the TN and HFS and require different treatment strategies. MRI scan is a necessary tool in the diagnostic complex, but its function is different and mentioned in the above paragraph. Of course, ectopic VA and/or BA and their relationship with the cranial nerves and the brainstem are always clearly visible on MRI. However, indications for surgical treatment are determined solely based on clinical manifestations of the
disease. Cranial nerve hyperfunction manifested as TN, HFS, and glossopharyngeal neuralgia is probably one of a few neurosurgical pathologies, where MRI is absolutely of secondary importance.

The authors described in detail and illustrated surgical technique of vascular decompression of the trigeminal and facial nerve. Importantly, the authors emphasized the need to create conditions for VA and BA transposition and maximum possible eliminations of the contact between the vessel and nerve. However, the preferential use of pieces of patient’s muscle or adipose tissue as the protector suggested by authors in most cases is difficult to agree. Our experience and numerous publications, which confirm the correctness of our choice, suggest that the use of synthetic material made of fluoropolymer (also known as Teflon) as a protector is highly effective. Protectors made of Teflon felt or wool provide adequate decompression of cranial nerves for a long time, while being absolutely biologically inert materials for the human.

Among other things, the authors made an important conclusion that protectors should be placed not only between the cranial nerve root, but also the brainstem. Our experience shows that it is more important for HFS, since hyperfunction of the facial nerve is often caused by irritation of its nucleus in the brain stem, namely the geniculate ganglion.

Brilliant results of surgical treatment carried out by the authors is worthy of every respect and show that release of the cranial nerves from the pulsating compression caused by VA or BA is not only possible, but also necessary in TN and HFS patients. It is also evidenced by the review of English-language literature on this subject, which is provided in the discussion and enhances the value of the article.

V.N. Shimanskiy (Moscow, Russia)
Hyponatremia is one of the most threatening systemic complications in neurosurgical patients, which requires close attention. This condition is characterized by a drop in Na serum levels below 135 mmol/L. In the absence of timely diagnosis and adequate treatment, hyponatremia can lead to serious complications. For example, according to G. Gill [1, 2] mortality of hospitalized patients with different pathologies and Na level below 130 mmol/L was identified (2% of all operated patients). Mortality in patients with hyponatremia was 14.3%, which is an order of magnitude higher compared to the rest of the population of patients without hyponatremia who were operated on during the same period. In adults, hyponatremia most frequently occurred after resection of craniopharyngiomas (11%) and as a result of acute cerebrovascular accident (22%). In children, it occurred after resection of craniopharyngiomas (10%), astrocytomas (7%), ependymomas (24%), and germ cell tumors (10.5%).

**Conclusion.** This study, which was mainly statistical one, was not aimed at detailed investigation of hyponatremia in different groups of neurosurgical patients. We only tried to draw the attention of various experts to those categories of patients, where focused and in-depth developments are more than important. Obviously, already gained international experience should be taken into account for this purpose. Therefore, this article presents the literature data on the etiology and pathogenesis of hyponatremia. We describe the details of the various classifications of hyponatremia, its clinical symptoms, diagnosis, and treatments, primarily based on the recommendations of the last European consensus of various specialists (2014).

**Keywords:** hyponatremia, brain tumors, neurosurgery, neurotrauma, SAH.

### Abbreviations

- ADH — antidiuretic hormone (vasopressin)
- ACTH — adrenocorticotropic hormone
- ACVI — acute cerebrovascular insufficiency
- VCF — volume of the circulating fluid
- SAH — subarachnoid hemorrhage
- CSA — chiasmosellar area
- CVP — central venous pressure
- CSW — cerebral salt wasting syndrome
- Na — sodium
- SIADH — syndrome of inappropriate antidiuretic hormone secretion
- V2-receptors — type-2 receptors of vasopressin

Hyponatremia is one of the most threatening systemic complications in neurosurgical patients, which requires close attention. This condition is characterized by a drop in Na serum levels below 135 mmol/L. In the absence of timely diagnosis and adequate treatment, hyponatremia can lead to serious complications. For example, according to G. Gill [1, 2] mortality of hospitalized patients with different pathologies and Na level of 120—125 mmol/L reaches 23%, whereas in those with Na level <115 mmol/L it reaches 50%. A prospective study of patients with various surgical pathologies and hyponatremia demonstrated that Na level <130 mmol/L is associated with 60-fold increase in the risk of serious complications (compared to patients without hyponatremia) and mortality among patients with Na level <120 mmol/L amounts to 25% in contrast to 9.3% in patients with Na levels >120 mmol/L [3].

Due to the urgency of the issue, hyponatremia has recently been attracting increased attention of experts from different fields of medicine. International and national guidelines for diagnosis and treatment of hyponatremia were published in the US [4], Spain [5], Sweden [6], and England [7] in 2013–2014 and recommendations are being developed for Italy and Norway [cit. ex 8].

Clinical practice guideline on diagnosis and treatment of hyponatremia was developed jointly by the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Association of Nephrology (ERA-EDTA) and was published in 2014; this is
the document we mainly relied upon in the writing of this article [9]. Given the differences in diagnosis and treatment criteria (for example, American and European guidelines recommend different rates of Na level increase, of achieving the target level of Na in the course of treatment, etc), the issue of hyponatremia remains to be highly relevant. In addition, in the aforementioned consensus the authors appeal to researchers, outlining specific tasks for new studies to compensate for the lack of prospective randomized studies on this topic in the literature.

In Russia, only a small number of papers in various fields of medicine is dedicated to the problem of hyponatremia [10—13], and the issues of hyponatremia in neurosurgery are described only in singular publications [14—16]. In the international recommendations, the differential diagnosis of hyponatremia is based only on the measurement of blood and urine osmolality and determination of Na level in the urine. Unfortunately, most medical institutions in Russia do not determine blood and urine osmolality. These studies are not routinely performed even in the major neurosurgical centers.

**Material and Methods**

To study the incidence of hyponatremia in neurosurgical patients, we retrospectively analyzed all 39,479 clinical cases of patients operated on at the Burdenko Neurosurgical Institute between January 2008 and December 2014. The study included all patients with moderate and severe hyponatremia (Na level <130 mmol/L). It did not include cases of mild hyponatremia (130—135 mmol/L).

We identified 785 patients (554 adults and 231 children) with hyponatremia whose Na level was <130 mmol/L, which amounted to 2% of the all operated patients.

The adult population included 257 men and 297 women aged 18 to 88 years (median age 53); the children population included 130 boys and 101 girls aged 3 months to 18 years (median age 4 years).

63% of patients (497 patients) had moderately decreased level of sodium (125 to 130 mmol/L), whereas in 11% of cases (88) the Na level was <120 mmol/L.

Mortality in this group of patients with hyponatremia was 14.3% (112 patients), whereas in the total cohort of patients operated on at the Burdenko Neurosurgical Institute during this period (7 years), the mortality was 10-time lower and amounted to 1.42% (563 cases). We reviewed the types of neurosurgical pathologies, which were the most common in this group of patients (Table 1).

The cohort of adult patients with hyponatremia predominantly had CSA tumors (28%), mainly pituitary adenomas (15.5%) and craniopharyngiomas (8.5%), meningiomas of the sella tubercle and the anterior cranial fossa (4.3%); meningiomas of other sites (12.3%), astrocytomas (6%), glioblastomas (8.8%), vascular pathologies, including aneurysms, SAH and ACVI (9.7%). Astrocytomas (30%) and craniopharyngiomas (17.7%) were the most common among children.

The results of our study are not consistent with the literature data, and it can primarily be attributed to small number of patients with such disorders as acute neurotrauma and SAH operated on at the Institute, due to particular pattern of admission to the Institute. It probably explains why, in contrast to the literature where the most frequently encountered patients with hyponatremia are those with SAH and acute neurotrauma, our population is dominated by patients after pituitary surgery.

We have analyzed the incidence of hyponatremia in a cohort of patients by the nosology (Table 2).

We have established that moderate and severe postoperative hyponatremia is frequently detected (in more than 5% of cases) in patients with craniopharyngiomas, CSA meningiomas, stroke, ependyrmomas and germinomas.

**Tables 3 and 4** present the most common types of pathologies complicated by postoperative hyponatremia in adults and children, respectively.

These data suggest that hyponatremia is most frequently observed in adults after the resection of craniopharyngiomas (11.3%) and as a result of ACVI (21.8%).

These data suggest that hyponatremia is most frequently observed in children after the resection of craniopharyngiomas (10%), astrocytomas (6.6%), ependymomas (24.1%), and germ cell tumors (10.5%).

**Discussion and recommendations for diagnosis and treatment**

As can be understood from the above, our study was mainly statistical in character and was not designed for detailed investigation of hyponatremia in different groups of neurosurgical patients. We have merely tried to draw the attention of relevant specialists to the categories of patients for whom focused and in-depth investigation is of the greatest importance. Naturally, one should take into account the existing international experience.

Hyponatremia develops in 10—20% of patients with various brain injuries [17]. For example, a decrease in Na blood levels is observed in 15—20% of patients with neurotrauma [18, 19] and almost a half of patients with subarachnoid hemorrhage [20, 21]. Typically, in these conditions hyponatremia is observed over 2—4 days and is associated with brain edema. Hyponatremia is common in surgery of CSA tumors, for example, in case of intersection of the pituitary stalk or surgical damage to the posterior section of the pituitary gland [22].

Hyponatremia can be described by various parameters. These include Na concentration, rate of hyponatremia development, severity of its symptoms, blood osmolality and degree of dehydration of the body. Hyponatremia can be classified in accordance with the above factors, each of which has its own advantages and disadvantages for a specific clinical situation. It should be noted that differential diagnosis of causes of hyponatremia is extremely difficult and there is no absolute differential diagnostic criterion.

Treatment tactics must be based on a combination of all of these criteria. According to the consensus of 2014, referred to in the introduction [9], the following criteria for hyponatremia are identified.

**1. Classification of hyponatremia based on Na blood level**

<table>
<thead>
<tr>
<th>Type of Hyponatremia</th>
<th>Blood Na Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;130 mmol/L</td>
</tr>
<tr>
<td>Moderate</td>
<td>125 to 130 mmol/L</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;125 mmol/L</td>
</tr>
</tbody>
</table>

Hyponatremia is considered to be mild at Na level in the blood of 130 to 134 mmol/L, moderate, at 125 to 129 mmol/L, and severe, at <125 mmol/L.

The definitions of mild, moderate and severe hyponatremia are not consistent in the published literature, and the threshold used to define severe hyponatremia ranges from 110 to 125 mmol/L [23, 24]. Some studies show that when Na
concentration falls below 125 mmol/L, the symptoms (Table 5) become more pronounced, and the correction to normal Na level requires constant monitoring in order to avoid too rapid ascent [cit. ex 9].

2. Classification of hyponatremia based on the duration of its development

Hyponatremia is considered to be acute if it has been proven that it developed less than 48 hours ago. Hyponatremia is considered to be chronic if it has been proven that it developed earlier than 48 hours ago. If the time of onset is unknown, hyponatremia is considered to be chronic.

Published studies suggest a threshold of 48 hours to distinguish acute and chronic hyponatremia. Cerebral edema occurs more frequently if hyponatremia develop in less than 48 hours [25, 26]. Experimental studies also suggest that the brain needs approximately 48 hours to adjust to hypotonic environment, mainly through the removal of Na and potassium ions, chlorides and osmotically active organic compounds from the brain cells [27, 28]. Prior to the adaptation, there is a risk of cerebral edema because low osmolality of the extracellular fluid contributes to the inflow of water into the cells. However, once the adaptation is completed, brain cells can be further affected if Na concentration rises too rapidly. Rupture of myelin sheath that envelops individual neurons can result in osmotic demyelination syndrome [29].

It is therefore important to distinguish acute and chronic hyponatremia to assess the risks of brain edema and osmotic demyelination [30]. Unfortunately, the difference between acute and chronic hyponatremia is often unclear in clinical practice, especially in patients admitted to the hospital since it is often unknown when Na concentration started to decline. If it is impossible to distinguish between acute and chronic hyponatremia, it is advisable to consider it to be chronic, because chronic hyponatremia is much more common than the acute one, and the principles of its treatment should be different to avoid osmotic demyelination.

3. Classification of hyponatremia severity of based on the symptoms

Hyponatremia with any biochemical profile is considered to be moderate if it is accompanied by moderate symptoms of hyponatremia. Hyponatremia with any biochemical profile is considered to be severe if it is accompanied by acute symptoms of hyponatremia (Table 5).

However, these symptoms are non-specific and can be due to other causes. Nonetheless, the symptoms that accompany cerebral edema are very likely to be associated with hyponatremia.

Classification of hyponatremia as “moderate” and “severe” based on the symptoms relies on mortality rate, which is higher in patients with acute symptoms. Moderate symptoms caused by brain edema are less frequently fatal. Nevertheless, they can quickly progress to severe symptoms, leading to death.

The latest recommendations by an expert group deliberately exclude asymptomatic hyponatremia, since such a definition may create confusion. Patients are almost never completely “asymptomatic” in the strict sense of the word. Very minor and subclinical symptoms are observed in case of mild hyponatremia [9].

4. Classification based on the osmolality of the serum

The following types of hyponatremia are identified based on the osmolality of serum: hypertensive (with hyperglycemia, after administration of mannitol), isotonic (pseudo-hyponatremia, introduction of hypoosmolar solutions) and hypotonic hyponatremia. In this article, we discuss only hypotonic hyponatremia.

5. Classification based of fluid volume

Patients with hyponatremia can be hypovolemic, euvolemic and hypervolemic [31]. Many traditional diagnostic algorithms start with a clinical assessment of blood volume [32]. However it is not always clear whether this volume reflects extracellular fluid, effective circulating volume or the entire

Table 1. Number of hyponatremia cases (Na<130 mmol/L) in adults and children with different neurosurgical pathologies operated on at the Burdenko Neurosurgical Institute (2008—2014)

<table>
<thead>
<tr>
<th>Neurosurgical pathology</th>
<th>Number of patients with hyponatremia (n=785)</th>
<th>Number of adults with hyponatremia (n=554)</th>
<th>Number of children with hyponatremia (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>102</td>
<td>33</td>
<td>69</td>
</tr>
<tr>
<td>Craniopharyngiomas</td>
<td>88</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>86</td>
<td>86</td>
<td>—</td>
</tr>
<tr>
<td>Meningiomas of sella tubercle</td>
<td>13</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>Meningiomas of the anterior cranial fossa</td>
<td>11</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Meningiomas of other sites</td>
<td>70</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>49</td>
<td>49</td>
<td>—</td>
</tr>
<tr>
<td>Metastases (mts) in the brain and spinal cord</td>
<td>26</td>
<td>26</td>
<td>—</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>25</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>21</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>ACVI</td>
<td>19</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>SAH</td>
<td>16</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>Consequences of TBI</td>
<td>21</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>ATBI</td>
<td>19</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Neurinomas</td>
<td>19</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Germinomas and germ-cell tumors</td>
<td>15</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Another pathology</td>
<td>185</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 2. Incidence of hyponatremia (Na<130 mmol/L) in patients with different neurosurgical pathologies operated on at the Burdenko Neurosurgical Institute (2008—2014)

<table>
<thead>
<tr>
<th>Neurosurgical pathology</th>
<th>Number of operated patients (n=39,479)</th>
<th>Number of patients with hyponatremia n=785</th>
<th>Number of patients with hyponatremia,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>2,074</td>
<td>102</td>
<td>4.9</td>
</tr>
<tr>
<td>Craniopharyngiomas</td>
<td>827</td>
<td>88</td>
<td>10.6</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>2,356</td>
<td>86</td>
<td>3.7</td>
</tr>
<tr>
<td>Meningiomas of CSA</td>
<td>844</td>
<td>24</td>
<td>6.3</td>
</tr>
<tr>
<td>Meningiomas of other sites</td>
<td>3,490</td>
<td>70</td>
<td>2.0</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>2,221</td>
<td>49</td>
<td>2.2</td>
</tr>
<tr>
<td>Metastases (mts) in the brain and spinal cord</td>
<td>1,046</td>
<td>26</td>
<td>2.5</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>170</td>
<td>25</td>
<td>14.7</td>
</tr>
<tr>
<td>Anceurysms</td>
<td>2,660</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>ACVI</td>
<td>79</td>
<td>19</td>
<td>24.1</td>
</tr>
<tr>
<td>SAH</td>
<td>546</td>
<td>16</td>
<td>2.9</td>
</tr>
<tr>
<td>Consequences of TBI</td>
<td>697</td>
<td>21</td>
<td>3.0</td>
</tr>
<tr>
<td>ATBI</td>
<td>402</td>
<td>19</td>
<td>4.7</td>
</tr>
<tr>
<td>Neurinomas</td>
<td>1,690</td>
<td>19</td>
<td>1.1</td>
</tr>
<tr>
<td>Germinomas and germ-cell tumors</td>
<td>186</td>
<td>15</td>
<td>8.1</td>
</tr>
<tr>
<td>Another pathology</td>
<td>20,191</td>
<td>185</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 3. Incidence of hyponatremia (Na<130 mmol/L) in adult patients with different neurosurgical pathologies operated on at the Burdenko Neurosurgical Institute (2008—2014)

<table>
<thead>
<tr>
<th>Neurosurgical pathology</th>
<th>Number of operated adults</th>
<th>Number of operated adults with hyponatremia</th>
<th>Number of operated adults with hyponatremia,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>1,027</td>
<td>33</td>
<td>3.2</td>
</tr>
<tr>
<td>Craniopharyngiomas</td>
<td>416</td>
<td>47</td>
<td>11.3</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>2,298</td>
<td>86</td>
<td>3.7</td>
</tr>
<tr>
<td>Meningiomas of CSA</td>
<td>844</td>
<td>24</td>
<td>2.8</td>
</tr>
<tr>
<td>Meningiomas of other sites</td>
<td>3,449</td>
<td>70</td>
<td>2.0</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>2,080</td>
<td>49</td>
<td>2.4</td>
</tr>
<tr>
<td>Metastases (mts) in the brain and spinal cord</td>
<td>1,010</td>
<td>26</td>
<td>2.6</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>116</td>
<td>12</td>
<td>10.3</td>
</tr>
<tr>
<td>Anceurysms</td>
<td>2,598</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>ACVI</td>
<td>78</td>
<td>17</td>
<td>21.8</td>
</tr>
<tr>
<td>SAH</td>
<td>532</td>
<td>16</td>
<td>3.0</td>
</tr>
<tr>
<td>Consequences of TBI</td>
<td>591</td>
<td>20</td>
<td>3.4</td>
</tr>
<tr>
<td>ATBI</td>
<td>366</td>
<td>18</td>
<td>4.9</td>
</tr>
<tr>
<td>Neurinomas</td>
<td>1,659</td>
<td>18</td>
<td>1.1</td>
</tr>
<tr>
<td>Germinomas and germ-cell tumors</td>
<td>77</td>
<td>4</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Table 4. Incidence of hyponatremia (Na<130 mmol/L) in children (under 18 years) with different neurosurgical pathologies operated on at the Burdenko Neurosurgical Institute (2008—2014)

<table>
<thead>
<tr>
<th>Neurosurgical pathology</th>
<th>Number of operated children</th>
<th>Number of operated children with hyponatremia</th>
<th>Number of operated children with hyponatremia,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>1,047</td>
<td>69</td>
<td>6.6</td>
</tr>
<tr>
<td>Craniopharyngiomas</td>
<td>411</td>
<td>41</td>
<td>10.0</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>41</td>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>54</td>
<td>13</td>
<td>24.1</td>
</tr>
<tr>
<td>Consequences of TBI</td>
<td>106</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurinomas</td>
<td>31</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>Germinomas and germ-cell tumors</td>
<td>105</td>
<td>11</td>
<td>10.5</td>
</tr>
</tbody>
</table>
volume of water in the body. In addition, sensitivity and specificity of clinical assessment of the volume are low, which can lead to misclassification in the earliest stages of the diagnostic tree. Therefore, we use the terms “effective circulating volume” and “extracellular fluid volume” in the text [9].

**Pathophysiological causes of hyponatremia in neurosurgical patients**

The pathophysiological mechanisms of hyponatremia in patients with acute brain damage cannot be attributed to one single cause; it is often a multifactorial process. Nevertheless the following principal causes of hyponatremia in neurosurgical patients are identified: syndrome of inappropriate secretion of antidiuretic hormone (SIADH), acute adrenal insufficiency, cerebral salt wasting syndrome (CSW), loss or excessive fluid administration (Table 6).

**Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)**

In normal situation, serum osmolality and volume of circulating blood are the main stimuli for the release of ADH. Upon an increase in serum osmolality, osmoreceptors in hypothalamus induce the secretion of ADH in the posterior pituitary gland. On the other hand, upon a decrease in intravascular volume, baroreceptors in carotid sinuses stimulate the release of ADH. In kidneys, ADH binds to V2-receptors and increases the permeability of the distal tubule and reabsorption of urine, leading to restoration of the intravascular volume. In SIADH, neither hyperosmolarity nor reduction in volume is an incentive for ADH secretion. The main pathophysiological cause of SIADH is the result of excessive ADH release irrespective of physiological osmotic stimuli, which is accompanied by inadequate fluid retention by kidneys (antidiuresis) and dissolution hyponatremia in clinically euvolemic patient.

ADH also regulates water balance and stabilizes osmotic pressure of the fluid in the brain at the cellular level [33]. Acute injury, ischemia or cerebral hypoxia leads to osmotic imbalance between the cell and the intercellular fluid. SIADH diagnostic criteria are presented in Table 7 [22, 33, 34].

**Adrenal insufficiency**

Biochemical characteristics of acute glucocorticoids deficiency are identical to those of SIADH. Patients with SIADH and hypocorticoidism have elevated levels of ADH. Additionally, cortisol itself is necessary for excretion of free water and it deficit promotes euvolemic hyponatremia [22, 34]. Therapy with glucocorticoid drugs inhibits the secretion of ADH and normalizes Na plasma concentration in patients with ACTH deficiency.

**Cerebral salt wasting syndrome (CSW)**

Cerebral salt wasting syndrome is an uncommon cause of hyponatremia in neurosurgical patients. This term was first proposed by J. Peters et al. in 1950 [35] and later it has been described in patients with different intracranial pathologies, including SAH [36, 37], TBI [38, 39], intracerebral tumors [40] and SCA tumors [41], ACVI [42]. One possible mechanism of its development is the disruption of renal sympathetic innervation in patients with cerebral pathology which causes excessive excretion of Na (natriuresis) and urine, resulting in hyponatremia and decreased CBV [36]. Basic diagnostic differences are presented in Table 8.

The main difference between SIADH and CSW is the fact that in CSW the loss of salts by the kidneys leads to the reduction in the circulating blood volume and hyponatremia whereas SIADH is an euvolemic condition. However, it is possible that natriuresis and diuresis, which are included in this syndrome, may be due to SIADH after an antidiuretic phase. Two recent large prospective studies of hyponatremia in patients with SAH and neurotrauma did not identify any cases of salt wasting syndrome [21, 43].

As can be seen from Table 8, in most cases the diagnostic criteria are non-specific, and since the central venous pressure measurement is performed mainly in intensive care units it makes the diagnosis in clinical departments extremely difficult.

**Hyponatremia in different neurosurgical pathologies**

**Hyponatremia after transsphenoidal surgery.** This pathology is described for 3–25% of patients in various series [45, 46]. The main cause of hyponatremia after the resection of a CSA tumor is SIADH. The presence of uncompensated hypopituitarism prior to the surgery increases the incidence of hyponatremia after the surgery [46]. Acute adrenal insufficiency as the cause of hyponatremia is ruled out for patients who routinely receive stress doses of glucocorticoids in the perioperative period.

Mechanical damage to the neurohypophysis or the pituitary stalk is the major factor in uncontrolled release of ADH. Transient hyponatremia after a pituitary surgery may be a component of a three-phase course of diabetes insipidus. The first phase is caused by damage to the pituitary stalk, ischemia, or edema of the hypothalamic-pituitary structures, or disruption of the venous outflow in the pituitary stalk and is characterized by acute symptoms of diabetes insipidus. It is followed by a period of hyponatremia caused by uncontrolled release of the accumulated ADH pellets from hypothalamic neurons due to their retrograde degeneration. The first phase of diabetes insipidus usually lasts for the first 48 hours after a surgery. The subsequent period of hyponatremia develops within a few days until all accumulated ADH pellets are “utilized”. This period is followed by the formation of gliosis of hypothalamic neurons which is accompanied by persistent phase of diabetes insipidus. Therefore, treatment of postoperative diabetes insipidus by analogues of vasopressin must be monitored hourly by measurements of urine output, since the prescription of obligated therapy with these drugs may aggravate subsequent hyponatremia phase.

**Hyponatremia in neurotrauma.** Approximately 15% of patients develop hyponatremia primarily within the first 5 days after a neurotrauma [18, 43]. In most cases, low concentrations of Na in the plasma are transient and regress spontaneously [38]. Previously, SIADH was thought to be the main cause of

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Nausea without vomiting</td>
</tr>
<tr>
<td></td>
<td>Decreased activity</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Severe</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Cardio-respiratory distress syndrome</td>
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<tr>
<td></td>
<td>Somnolence</td>
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<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Coma (at Glasgow ≤ 8 scale)</td>
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</table>
hyponatremia in TBI, and acute ACTH deficiency was considered to be a rare cause. However, most previous studies were based on a single assessment of cortisol level, whereas its level in the blood plasma is extremely unstable and, therefore, the reports based on a single hormone assessment can overlook the role of pituitary dysfunction in the development of hyponatremia after TBI [cit. ex 22].

A recent prospective study has found hyponatremia and acute adrenal insufficiency in a large cohort of patients with TBI [43]. In this study, 15% of patients had transient hyponatremia. Comparison of Na levels in patients with TBI in a group of critically ill patients without neurotrauma revealed that 87% of patients with neurotrauma had low plasma concentration of cortisol. Parenteral administration of hydrocortisone resulted in normalization of Na levels in all patients. No cases of CSW were observed [21]. Therefore, acute ACTH deficiency may play an important role in the development of hyponatremia after TBI. The presence of arterial hypotension and/or hypoglycemia is an indirect symptom of secondary adrenal insufficiency, especially in combination with hyponatremia. Chronic hyponatremia is a rare condition in TBI and is likely to be due to other causes (e.g., anticonvulsant therapy [cit. ex. 22]).

Hyponatremia as a consequence of SAH. According to the literature [22], hyponatremia occurs much more frequently in patients with SAH in comparison to patients with other neurosurgical pathologies and is detected in approximately 50% of patients. Causes of hyponatremia in patients with SAH are varied and include SIADH, acute adrenal insufficiency, CSW, and other reasons. Some studies [47, 48] believe that CSW is the main cause. According to one hypothesis, vasospasm is the most common cause of hyponatremia in SAH. The blood enters the subarachnoid space after a rupture of an aneurysm, while the release of hemolysis products results in a release of vasoactive substances and initiation of pathophysiological process that includes a spasm of the main branches of the circle of Willis. Vasospasm can lead to a marked reduction in cerebral blood flow, delayed cerebral ischemia and, as a result, to abnormal hormone secretions and hyponatremia. A paper by T. Zhang et al. [49] examined 49 SAH patients and found that cerebral vasospasm rates were significantly higher in patients with hyponatremia. Early deceleration of natriuresis by fludrocortisone prior to manifestations of hyponatremia prevented the onset of vasospasm after SAH. The authors propose to start fludrocortisone therapy in patients with SAH in case of increased excretion of Na with the urine. Hyponatremia is more common in case of SAH from the anterior communicating artery (51%), whereas the damage to the middle cerebral artery is associated with only 18% incidence. The presence of hyponatremia may be a predictor of the risk of vasospasm and cerebral ischemia [50—52].

However, according to different authors, the causes of hyponatremia in SAH remain unclear. In a retrospective study L. Kao et al. [20] examined patients with Na level <130 mmol/L and found that in 35% of cases the cause of hyponatremia was SIADH and in 22.9% it was CSW. The disadvantage of the majority of retrospective studies is the lack of routine assessment of cortisol level dynamics in the blood. In their studies, M. Klose et al. [53] and G. Parenti et al. [54] demonstrated that 7.1 to 12% of patients with SAH have cortisol deficiency. In the largest prospective study, hyponatremia was observed in 49% of patients with SAH; the most frequent cause was SIADH (71.4%), 8.2% of patients with hyponatremia had an acute ACTH deficiency; and there were no cases of CSW [21]. The causes and pathophysiological process of hyponatremia in SAH is insufficiently studied and to date there is no standardized treatment. Hyponatremia may occur in other CNS disorders, but much less frequently than in TBI, SAH and pituitary surgery, and often its cause is the irritation of the pituitary stalk or acute secondary or tertiary adrenal insufficiency as a result of cerebral edema caused by surgical intervention, regardless of the primary pathology.

Diagnosis of hyponatremia. The international consensus of 2014 [9] provides diagnostic algorithm for hyponatremia for various conditions and diseases that can be accompanied by hyponatremia (see Figure).

We have identified the main stages that are most important in the diagnosis of the causes of hyponatremia in neurosurgical patients.

1. It is recommended to exclude hyperglycemic hyponatremia by measuring blood glucose levels and to recalculate Na levels in blood in accordance with the glucose level if the latter is increased. Hyponatremia with the measured osmolality <275 mOsm/kg always points to hypotonic hyponatremia.

In clinical practice, in patients with diabetes decompensation the assessment of Na serum levels should be corrected for the presence of hyperglycemia and can be obtained from the following equations:

\[
\text{True } [\text{Na}^+] = \frac{\text{glucose (mmol/L)} - 5.5\text{ (mmol/L)}}{5.5\text{ (mmol/L)}} \times 2.4 + \text{Measured } [\text{Na}^+] + 2.4
\]

It means that it is necessary to add 2.4 mmol/L to the measured level of sodium per each 5.5 mmol/L (100 mg/dL) excess of glucose above standard serum glucose level of 5.5 mmol/L (100 mg/dL).

<table>
<thead>
<tr>
<th>Table 6. Etiology, diagnosis and treatment of hyponatremia in neurosurgical patients [cit. ex 22]</th>
</tr>
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<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>SIADH</td>
</tr>
<tr>
<td>Acute adrenal insufficiency</td>
</tr>
<tr>
<td>CSW</td>
</tr>
<tr>
<td>SIADH and CSW</td>
</tr>
<tr>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Excessive administration of fluids</td>
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Table 7. Diagnostic criteria for SIADH

<table>
<thead>
<tr>
<th>Essential criteria:</th>
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<tbody>
<tr>
<td>— Serum osmolality &lt;275 mOsm/kg</td>
</tr>
<tr>
<td>— Urine osmolality &gt;100 mOsm/kg</td>
</tr>
<tr>
<td>— Clinical euvolemia (or hypervolemia)</td>
</tr>
<tr>
<td>— Na urine levels &gt;30 mmol/L with normal dietary salt and water intake</td>
</tr>
<tr>
<td>— Absence of renal insufficiency</td>
</tr>
<tr>
<td>— Absence of adrenal, thyroid, pituitary or renal insufficiency or compensation</td>
</tr>
<tr>
<td>— No recent use of diuretic agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplemental criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Serum uric acid &lt;0.24 mmol/l (&lt;4 mg/dL)</td>
</tr>
<tr>
<td>— Serum urea &lt;3.6 mmol/l (&lt;21.6 mg/dL)</td>
</tr>
<tr>
<td>— Failure to correct hyponatraemia after 0.9 % saline infusion</td>
</tr>
<tr>
<td>— Fractional Na excretion &gt;0.5%</td>
</tr>
<tr>
<td>— Fractional urea excretion &gt;55%</td>
</tr>
<tr>
<td>— Fractional uric acid excretion &gt;12%</td>
</tr>
<tr>
<td>— Correction of hyponatraemia through fluid restriction</td>
</tr>
</tbody>
</table>

Table 8. Differences between SIADH and CSW [17, 22, 44]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SIADH</th>
<th>CSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of blood urea</td>
<td>Normal-low</td>
<td>Normal-high</td>
</tr>
<tr>
<td>Level of blood uric acid</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urine volume</td>
<td>Normal-low</td>
<td>High</td>
</tr>
<tr>
<td>Level of urinary Na</td>
<td>&gt;30 mmol/L</td>
<td>&gt;30 mmol/L</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Кровяное давление</td>
<td>Normal</td>
<td>Normal, orthostatic hypotension</td>
</tr>
</tbody>
</table>

2. Assessment of the main parameters to determine the cause of hypotonic hyponatremia. It is recommended to begin with assessment of osmolality of single portion of urine as the first step.

— For osmolality <100 mOsm/kg, it is recommended to consider relative excess of water intake as the cause of hypotonic hyponatremia.

— For osmolality >100 mOsm/kg, it is recommended to assess Na level in the urine from a single sample, taken simultaneously with the blood assay.

— For Na level in the urine <30 mmol/L, low effective arterial volume should be considered as the cause of hypotonic hyponatremia.

— For Na level in urine >30 mmol/kg, the state of the extracellular fluid and the use of diuretics should be evaluated for further diagnosis of the probable causes of hyponatremia.

— We do not recommend vasopressin study to confirm SIADH.

If there is no apparent increase in clinical volume of the extracellular fluid and the level of Na in urine is >30 mmol/L, it is advisable to rule out other causes of hypotonic hyponatremia prior to diagnostics of SIADH.

**Treatment of hyponatremia**

Treatment recommendations are developed in accordance with the hypothesis that in case of acute symptoms (vomiting, somnolence, seizures, coma, cardiorespiratory distress syndrome), the risk of cerebral edema is higher than the risk of osmotic demyelination syndrome. Therefore, urgent treatment is warranted regardless of Na level or time period for development of hyponatremia (acute or chronic).

Hyponatremia in combination with acute symptoms is life-threatening and requires emergency medical care.

On the contrary, in the absence of acute symptoms there is time for diagnostic evaluation and selection of pathogenetic treatment based on the cause of hyponatremia.

On the other hand, the treatment itself is potentially hazardous as rapid correction of Na levels can cause osmotic demyelination. Rapid correction of Na level results in rapid recovery of Na and K levels in a cell, whereas the recovery of dissolved organic matter may take 5—7 days. This leads to the inflow of water from the cells into the myelin sheath of nerve cells, swelling of the membranes, osmotic damage to the endothelial cells, local release of factors toxic for myelin and oligodendrocyte death [55]. These changes develop within 2—3 days from the beginning of the rapid correction.

Osmotic demyelination is a dangerous condition which is clinically characterized by the development of spastic tetraparesis, cranial nerve palsy, dysphagia, psychopathological symptoms. Osmotic demyelination mainly affects the brain stem, but in 10% of cases it also affects cerebellum, thalamus, midbrain and lateral geniculate body [4]. The risk is particularly high in case of rapid correction of Na levels. Diagnosis of osmotic demyelination is based on clinical symptoms and MRI characteristics that have the classic manifestations: high signal areas around the bridge in T2-weighted mode and low signal in T1-mode. The prognosis varies, but is generally unfavorable.

In our review, we provide step by step recommendations for emergency treatment of hyponatremia with acute symptoms. Principles of treatment of patients with chronic hyponatremia are detailed in the international consensus on the treatment of hyponatremia [9].
Treatment of hyponatremia with acute symptoms in neurosurgical patients

There is a need for rapid initial correction to reduce brain edema. It has been shown that the use of hypertonic solution and increase of Na plasma level by 5 mmol/L can reduce intracranial pressure and eliminate neurological symptoms of cerebral edema by ca. 50% within 1 hour [56].

Therefore, the proposed approach for correction of hyponatremia with neurological symptoms is the initial increase in Na plasma level by 5 mmol/L, over 1 hour.

The second recommendation is to set the target limit on the increase of Na plasma level. Given the rare reported cases of osmotic demyelination after increasing Na plasma concentration by 10 mmol/L, it is currently recommended to increase Na level by less than 10 mmol/L over 24 hours.

Thus, the recommended treatment regimen consensus is as follows.

1. Immediate start of the treatment (within the first hour of identifying hyponatremia), irrespective of the time of onset:
   — Emergency i/v administration of 150 ml of 3% NaCl or its equivalent for 20 minutes. Na levels must be checked after 20 minutes, and, if necessary, the administration of 150 ml of 3% NaCl must be repeated for the next 20 min;
   — Repeated administration to increase Na levels in the blood by 5 mmol/L. Patients with acute symptomatic hyponatremia must be treated in a hospital where they can receive proper biochemical and clinical monitoring.

2. Follow up management in case of improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of the time of onset:
   — Discontinue administration of 3% NaCl;
   — Continue i/v administration of small volume of 0.9% NaCl until initiation of etiopathogenetic treatment;
   — Initiate treatment focused on the established diagnosis, if possible, and try to stabilize at least the level of Na;
   — Limit the increase of Na blood level by 10 mmol/L in the first 24 hours and 8 mmol/L per the following 24 hours, until Na reaches the level of 130 mmol/L;
   — Measure Na level after 6 and 12 hours every day until it is stabilized.

3. Follow up management in case of no improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of the time of onset:
   — Continue i/v administration of 3% NaCl or its equivalent in order to increase Na level by 1 mmol/L per hour;
   — Discontinue administration of 3% NaCl or its equivalent if the symptoms regress, Na level increases by 10 mmol/L overall or the level of 130 mmol/L is reached;
   — Exclude the presence of other conditions with a clinical presentation similar to hyponatremia;
   — Check Na level every 4 hours when administering 3% NaCl or its equivalent.

4. For patients with low circulating volume:
   — Restore extracellular volume by infusion of 0.9% NaCl or balanced crystalloid saline solution at a dose of 0.5—1.0 ml/kg/h;
   — Treat patients with unstable hemodynamics in an intensive care unit;
   — In case of unstable hemodynamic the benefits of ongoing rehydration are greater than the risk of too rapid increase in the level of Na.

5. What to do in case hyponatremia is corrected too rapidly?
   — Reduce Na level if it increased by more than 10 mmol/L in the first 24 hours or by more than 8 mmol/L in every subsequent 24 hours by i/v administration of 10 mL per 1 kg body weight of 5% glucose solution for 1 h under the strict control of diuresis and fluid balance;
   — Possible option is i/v administration of 2 mg of desmopressin strictly as a single dose no more often than once in 8 hours.

Treatment of chronic hyponatremia in neurosurgical patients

Treatment varies based on the pathogenesis of hyponatremia.

1. Treatment of SIADH

In case of moderate or severe hyponatremia, restrict fluid intake, use urea solution in a dose of 0.25—0.50 g/kg of urea per day or combination of low oral doses of loop diuretics and sodium chloride.

Antagonists of vasopressin receptors are not recommended in case of moderate hyponatremia.

Antagonists of vasopressin receptors are recommended in case of severe hyponatremia.

Patients after neurosurgery may require infusions and, consequently, restriction of the fluid intake is often impossible.

Demeclocycline, which has been well established in treatment of SIADH, have no registered indications for this syndrome. Furthermore, it is nephrotoxic and can cause photosensitive skin rashes.

Urea has been shown to be effective in treatment of SIADH. A recent retrospective uncontrolled study of treatment outcomes in patients at SIADH in SAH showed that urea therapy led to normalization of Na levels, at low cost and with no significant side effects [57]. However, Na plasma levels normalized over an average of 3 days on urea treatment. Since an average duration of hyponatremia in SAH is 3 days, it remains unclear whether this is a genuine normalization effect of urea treatment. Urea has registered indications, however, except for some European centers, such as Belgium, the experience of the use of urea in neurosurgical patients is limited.

Tablets of sodium, fludrocortisone and loop diuretics are used to treat SIADH, but there is no physiological justification for their use [58].

Currently a new class of drugs, vasopressin receptor antagonists (vaptans), is proposed for treatment of SIADH. They bind to V2-receptors, mediate the response: prevent the binding of vasopressin, thus causing aquaresis (selective water diuresis) without affecting Na and potassium excretion. A study that used vaptans to treat SIADH after TBI found that they quickly and safely normalize Na plasma levels without any serious side effects [59]. However, currently there are no comparative studies on the effectiveness of vaptans and traditional methods of SIADH treatment in neurosurgical patients.

2. Treatment of CSW

Specific therapy for CSW is intravenous administration of 0.9% NaCl solution.
Hyponatremia

Exclude hyperglycemia and other causes of non-hypotonic hyponatremia

Hypotonic hyponatremia

Acute or severe symptoms?

Yes

Immediate treatment with hypertonic saline

No

Urine osmolality

≤100 mOsm/kg

Options:
- primary polydipsia
- low intake of salt
- beer potomania

> 100 mOsm/kg

Urine sodium concentration

≤30 mmol/L

Low CBV

If the extracellular fluid is expanded:
- heart failure
- cirrhosis
- nephrotic syndrome

> 30mmol/L

Diuretics or kidney disease?

Yes

Options:
- diuretics
- kidney disease

No

If the extracellular fluid is reduced:
- vomiting
- primary adrenal failure
- renal salt loss
- CSW
- diuretics of unknown origin

- all other causes

If the extracellular fluid is normal:
- SIAD
- secondary adrenal failure
- hypothyroidism
- diuretics of unknown origin

Diagnostic algorithm for hyponatremia [cit. ex. 9].

3. Treatment of hyponatremia in adrenal insufficiency

In case of clinical symptoms of adrenal insufficiency (arterial hypotension and/or hypoglycemia) and/or drop in morning levels of cortisol below 10.8 µg/L (300 nmol/L), it is recommended to initiate parenteral glucocorticoid therapy, which results in rapid normalization of Na blood levels in patients with ACTH deficiency [21, 22].
Introduction

Hyponatremia is associated with increased morbidity and mortality in neurological patients. Most often it affects patients with neurotrauma, SAH and SCA tumors. The most common causes of hyponatremia in this cohort of patients are syndrome of inappropriate secretion of ADH and acute adrenal insufficiency, less often, cerebral salt wasting syndrome. Although hyponatremia in SIADH may be accompanied by mild symptoms, merely limiting fluid intake is inefficient in most cases. Recently, a new class of drugs, vaptans, has been introduced to the market and has been shown to be effective in patients with SIADH, but these drugs are currently not approved in Russia. The method of choice for treatment of acute hyponatremia is immediate administration of a hypertonic solution. Diagnosis and treatment of hyponatremia present considerable complexity and should be performed in specialized centers by qualified personnel.

It is necessary to conduct further research to study pathogenesis of hyponatremia and to refine algorithms of its diagnosis and treatment in case of different neurological pathologies.

Authors declare no conflict of interest.

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Hyponatremia is rather common disruption of water-electrolyte balance with wide spectrum of clinical manifestations, up to critical condition and death of a patient due to brain edema. It occurs in patients suffering from variety of diseases, including those with brain lesions.

The article presents a large-scale retrospective analysis of 39,479 medical histories of all patients operated on at the Institute of Neurosurgery over the last 7 years. Of them, 785 cases were identified as requiring treatment of hyponatremia. The main types of neurosurgical pathologies that are most commonly associated with hyponatremia in children and adults were identified.

Therefore, the authors have conducted a large-scale research, over the course of which they identified particularly problematic types of neurosurgical pathologies associated with the greatest risk of hyponatremia. It creates foundation for further studies on the topic, identification of the causes that lead to this complication, and formulation of principles of its pathogenetic treatment.

Commentary

The article very appropriately uses the latest data of the European and American consensus for hyponatraemia, its diagnosis and treatment.

The presented stepwise algorithm of the initial emergency care for patients with acute hyponatremia, which is based on the analysis of a large number of publications and confirmed by the authors’ own experiences, is very important for clinicians.

We have to agree with the conventional opinion that the understanding of hyponatremia is still far from being complete. From the neurosurgical perspective, its further study should be aimed at clarifying the mechanisms of hyponatremia development in neurosurgical patients and methods of early prevention and treatment.

I believe that the publication of this article is very relevant and is of great scientific and practical importance.

V.S. Pronin (Moscow, Russia)
Basal Ganglia Germinomas in Children. Four Clinical Cases and a Literature Review


Burdenko Neurosurgical Institute, Moscow, Russia

Basal ganglia germinomas are a specific group of intracranial germinomas. Their early diagnosis is complicated due to their atypical localization and diversity of neuroimaging and clinical signs. Material and methods. We describe 4 cases of basal ganglia germinoma in boys of 13, 14, 15, and 16 years of age. The medical history data, clinical features, neuroimaging and histological characteristics of basal ganglia germinomas, and preliminary results of the treatment are presented. Conclusions. Basal ganglia germinomas are usually verified at the late stage of the disease when patients are detected with extended lesions of the basal ganglia and severe neuroendocrine and neurological deficits. This situation is associated with clinical and imaging signs that are atypical of common germinomas.

Keywords: basal ganglia germinoma, clinical signs, diagnosis.

Intracranial germinomas account for up to 0.5—2.1% of primary brain tumors [1—3]. In most cases, the disease develops in male adolescents, occurring several times more often in the Asian population than in the European one. Germinomas are usually localized in the pineal or suprasellar regions [2, 4]. The dominant symptoms usually include vision impairment and endocrine disorders if the disease is localized in the chiasm-sellar region, and symptoms of intracranial hypertension and midbrain lesions (Parinaud syndrome) when the disease is localized in the pineal region. However, germinomas have an unusual localization in the basal ganglia in 5—10% of cases [5, 6].

Germinomas are characterized by a variety of MRI manifestations — from subtle diffuse changes in the MRI signal to a large delineated space-occupying lesion uptaking a contrast agent [6—9]. Diagnosis of basal ganglia germinomas is often difficult. This is due to the localization and clinical signs atypical of this pathology. MRI at the early disease stage may miss the pathology, or the tumor looks like small lesions similar to foci of demyelination or ischemia. This is often the reason for the late diagnosis of basal ganglia germinomas [3, 9].

If germinoma is suspected, surgical treatment is limited to interventions aimed at sampling histological material and resolving intracranial hypertension because the tumor is highly sensitive to radiotherapy and chemotherapy.

The prognosis for germinomas is favorable, with the overall five-year survival rate amounting to >90% [1, 4]. In the case of small germinomas of the suprasellar localization with a short disease history, many of the clinical disease symptoms regress after treatment. In particular, patients may develop vision improvement and recovery of the pituitary function. However, treatment outcomes for germinomas of an atypical localization are worse: neurological symptoms can persist after achieving disease remission, which is a consequence of the late diagnosis [9]. In this connection, the early diagnosis and correct approach to treatment of suspected basal ganglia germinoma are of great importance.

Here, we present 4 clinical cases of basal ganglia germinomas in children, which were verified by stereotactic biopsy (STB) and open tumor biopsy.

Case 1

A 15-year-old male patient Z. was sick since 2009 (since the age of 10 years) when he developed headaches, recurrent vomiting, transient weakness in the right extremities, thirst, and polyuria of up to 10 liters per day. An examination at the place of residence revealed hearing loss on the right and diabetes insipidus. MRI of the brain in 2009 did not detect any pathology (Fig. 1). The patient was prescribed desmopressin.

Two years later (2011), the patient developed a transient tremor of the right arm, dysarthria, disrupted behavior, and reduced self-criticism. In 2012, the patient experienced weakness of the facial muscles on the right, muscle weakness and decreased sensation in the right extremities, fatigue, and headache episodes accompanied by nausea and vomiting. Two episodes of generalized convulsions were observed in February 2013. MRI of the brain (February 2013) revealed a space-occupying lesion of the basal ganglia on the left. In May 2013, the patient was hospitalized to the Neurosurgical Institute for stereotactic biopsy of a diffuse tumor of the basal ganglia and verification of the diagnosis. An endocrinological examination revealed, in addition to diabetes insipidus, panhypopituitarism (growth hormone deficiency, secondary hypothyroidism, hypocortisolism, hypogonadism) and hyperprolactinemia. The patient received replacement therapy with hydrocortisone and L-thyroxine. Given the characteristic endocrinological symptoms, a germinal tumor was suspected. However, a repeated MRI examination detected a decrease in the lesion size and increased strength in the right arm and leg. No signs of infiltration of the pituitary funnel or stalk were detected; signs of a partially empty sella were observed (Fig. 2). The cause of this phenomenon was not clear because the patient did not receive hormone therapy.
Given the MRI-revealed positive changes, the patient was discharged for further follow-up.

Since January 2014, right hemiparesis was worsened. MRI of the brain (June 2014) revealed a significant increase in the size of a basal ganglia tumor on the left (Fig. 3a–c) as well as foci of an altered T2 signal in the pituitary funnel projection, without clear accumulation of a contrast agent (Fig. 3d).

The clinical picture at admission to the Neurosurgical Institute demonstrated decreased muscle strength in the right extremities to 3 points, impaired surface sensitivity on the right, central type paresis of the facial nerve on the right, deafness on the right; neuroendocrine symptoms in the form of panhypopituitarism and diabetes insipidus; emotional and personality disorders in the form of reduced self-criticism, disinhibition, and euphoria. Levels of blood tumor markers AFP and b-hCG were within reference values.

The patient underwent stereotactic biopsy of the tumor. The histological diagnosis was germinoma. Positive expression of PLAP (placental alkaline phosphatase) and SD117 and negative expression of AFP and hCG were detected (Fig. 4).

The patient received 4 cycles of polychemotherapy according to the protocol “Germinoma-2008” (80 mg/m² of etoposide, days 1–4; 25 mg/m² of cisplatin, days 1–4) and negative expression of AFP and hCG were detected (Fig. 4).

According to the neurological status, an increase in the strength of the right arm and leg was observed. Control MRI revealed a complete involution of the tumor and atrophic changes in the subcortical region on the left (Fig. 5).

Brain tissue atrophy was observed at the site of a basal ganglia germinoma lysed due to chemotherapeutic therapy.

**Case 2**

A 13-year-old male patient E. was followed-up by a neurologist because of psychomotor retardation since an early age. Ambiopia developed in March 2012. The patient underwent first MRI in August 2012, which revealed no pathology. Planned MRI in January 2013 revealed a minor change in the signal in the left subcortical region. At that time, transient mild weakness in the right arm and leg developed. The patient was followed-up at the place of residence. In autumn 2013, thirst, polyuria of up to 9 liters per day, and weight loss developed. The patient was examined by a local endocrinologist who excluded diabetes mellitus and did not diagnose diabetes insipidus. Compulsive movements in the right arm developed since January 2014. Control MRI (June 2014) revealed a tumor lesion of the subcortical structures on the left (Fig. 6). An examination at the Neurosurgical Institute detected: right hemiparesis (4 points); right extrapyramidal symptoms in the form of involuntary athetoid-like movements of the right extremities; behavioral disorders in the form of disinhibition, foolishness, reduced self-criticism, and euphoria; neuroendocrine symptoms (diabetes insipidus, secondary hypocortisolism, growth hormone deficiency). The patient received replacement therapy with desmopressin and hydrocortisone, which resulted in a significant improvement in the general patient’s state. Blood tumor markers (AFP and b-hCG) were within the normal range.

The patient underwent stereotactic biopsy of the tumor. The histological diagnosis was as follows: small fragments of glial tissue with lymphoid infiltrates and single large cells expressing PLAP and SD117. Expression of AFP and b-hCG was negative. The morphological picture corresponded to germinoma.

A diffuse neoplastic lesion was observed in the lenticular nucleus region. The lesion had a hypointense T1 signal (a) and a hyperintense T2 signal (b). The tumor had focal accumulations of a contrast agent (c). The pituitary stalk was not thickened (d).

The patient was transferred to a specialized department for chemotherapy. Control brain MRI after the second cycle of chemotherapy revealed a significant reduction in the tumor size (Fig. 7).

A significant reduction in the basal ganglia tumor on the left and formation of a replacing CSF cyst were observed in association with administered chemotherapy.

**Case 3**

A 14-year-old male patient Z. developed involuntary movements of the right foot toes in summer 2006. In November 2006, the patient had episodes of weakness in the right extremities. Also, general weakness, fatigue, and drowsiness developed over time. MRI of the brain (December 2006) revealed a bilateral space-occupying lesion of the basal ganglia, with a large node on the right. Worsening of cerebral symptoms and recurrent vomiting developed over time. Somewhat later, the patient stopped talking and experienced increased weakness in the right extremities. The patient underwent decongestant and dehydration therapy at the place of residence. Control CT and MRI studies revealed an increase in the basal ganglia tumor size, expansion of the ventricular system, and periventricular edema (Fig. 8a, b).

There were detected bilateral tumors of the basal ganglia with a large node in the projection of the anterior thalamus and right caudate nucleus head and with a small node in the left lenticular nucleus. The tumors had a heterogeneous structure with hemorrhagic foci and calcifications. The tumors intensively accumulated a contrast agent. The ventricular system was expanded, with periventricular edema (a, b). Postoperative CT (c)

Figure 1. T2-weighted MRI in the axial plane. There are no pathological signs.
Figure 2. MRI reveals a small lesion with a hypointense T1 signal (a) and a hyperintense T2 signal (b) in the lenticular nucleus projection on the left. Minor contrast agent uptake is observed (c). The pituitary stalk is not changed (d).

revealed total resection of the right tumor and a small calcificated tumor on the left. The ventricular system decreased in size.

The clinical picture at admission to the Neurosurgical Institute (March 2007) was as follows: pronounced hypertensive syndrome with choked disks; tetraparesis, more pronounced on the right; extrapyramidal syndrome in the form of increased muscle tone in the right extremities (of the plastic and “thalamic hand” type on the right) and intention tremor on the left; hyperthermia, speech disorder in the form of motor aphasia, and pseudobulbar disorders. Polyuria was not observed. Blood tumor markers were not analyzed.

Given the condition severity caused by a large tumor of the basal ganglia, the patient underwent surgery for resecting a tumor of the basal ganglia region on the right, fornix, and interventricular septum.
Figure 3. Basal ganglia germinoma on the left.

a — T2-weighted MRI in the axial plane. A diffuse space-occupying lesion with a hypointense T1 signal is seen in the projection of the lenticular nuclei on the left. Infiltration of the internal capsule is observed; b — the tumor has a hyperintense FLAIR signal; c — an introduced contrast agent is heterogeneously accumulated; d — T1-weighted MRI in the sagittal plane reveals thickening of the pituitary stalk.
Germinoma is a two-cell type tumor composed of large light cells and focal clusters of lymphoid cells. Large cells are immunopositive for PLAP and CD117 (c-kit).

- a — germinoma, hematoxylin and eosin staining, magnification of 200×;
- b — immunohistochemistry with the PLAP antibody, magnification of 100×;
- c — immunohistochemistry with the CD117 antibody, magnification of 300×.

Germinoma was histologically diagnosed. An immunohistochemical examination revealed positive expression of PLAP and expression of human chorionic gonadotropin in single tumor cells (Fig. 9).

A blood test for tumor markers revealed an increased b-hCG level of 85.5 mIU/mL. The CSF b-hCG level was also elevated to 142.6, the AFP level was 1.4. Given the histological examination and increased b-hCG levels in the blood and cerebrospinal fluid, germinoma with a syncytiotrophoblastic component was diagnosed.

Postoperative CT of the brain revealed total tumor removal on the right and a small residual petrified tumor on the left (Fig. 8c).

In the postoperative period, the patient’s condition improved; the activity level increased; retardation regressed.
According to the neurological status, supranuclear impairment of pharynx innervation regressed to a large extent; the patient returned to self-feeding. The range of voluntary movements of the extremities increased. Right hemiparesis and extrapyramidal symptoms on the right persisted.

Surgery was followed by chemotherapy and a course of radiation therapy. According to relatives, there was no tumor recurrence for 7 years after treatment. The patient’s condition was stable. Tetrasyndrome, more pronounced in the right extremities, persisted. The patient could walk with support and care himself.

**Case 4**

A 16-year-old male patient Zh. was admitted to the Neurosurgical Institute in February 2004.

Behavioral changes occurred for three years before admission. Then, episodes of motor anxiety and hyperkinesis in the extremities as well as facial asymmetry developed. Several months before hospitalization, numbness and weakness in the right arm and then right-sided hemiparesis developed. MRI of the brain revealed signs of a cystic tumor of the basal ganglia on the left.

*Figure 6. Basal ganglia germinoma on the left.*
The clinical picture on an examination performed at the Neurosurgical Institute revealed emotional-mnestic disorders, elements of motor aphasia, right-sided pyramidal syndrome in the form of hemiparesis with reduced muscle strength up to 3 points, central paresis of the facial nerve, and impaired surface sensitivity on the right. There were no discernible neuroendocrine symptoms.

Brain MRI revealed a heterogeneous tumor of the left basal ganglia (Fig. 10a). Tumor markers were not tested.

Given the presence of a large cystic tumor causing significant neurologic disorders, the tumor was resected through the frontal transcortical approach (March 2004).

Germinoma was diagnosed histologically.
The postoperative period was uneventful. There was no worsening of focal symptoms. Control CT of the brain revealed partial removal of the tumor.

Given the tumor histology, the first course of chemotherapy was performed at the Neurosurgical Institute. In this connection, strength of the right extremities increased; a CT examination revealed a decreased residual tumor. After discharge from the hospital, the patient received comprehensive adjuvant treatment. MRI one year later revealed no signs of tumor recurrence (Fig. 10b). There was no tumor recurrence 10 years after the end of treatment.

Discussion

High sensitivity of germinomas to radiation therapy and chemotherapy limits surgery of these deep-seated tumors to sampling of biopsy material and operations aimed at elimination of intracranial hypertension. A timely diagnosis and an early onset of treatment can result in partial or complete regression of preoperative symptoms. This necessitates the early diagnosis of germinomas, which is usually not difficult in the case of a “typical” location of the tumor in the pineal and suprasellar regions.

Basal ganglia germinomas are rare. For this reason, the histological diagnosis is often unexpected if the tumor is localized in this region.

Typical manifestations of basal ganglia tumors, including germinomas, are symptoms of lesions of the internal capsule and basal ganglia (hemiparesis, extrapyramidal syndrome). In all our cases, hemiparesis of varying severity and extrapyramidal symptoms were present. In this case, hemiparesis regressed only partially or not regressed at all despite stable remission of the disease during treatment. This is associated with infiltrative growth of germinomas, a usually late diagnosis of the disease, and a late onset of therapy. In one of our cases, hemiparesis at the early stage of disease had a transitory nature, which caused a delay in stereotactic biopsy and further worsening of symptoms.

Diabetes insipidus is often the first and only symptom associated with suprasellar germinomas; in some cases, it develops before MRI visualization of the tumor [11, 12]. In our study, diabetes insipidus in case 1 was diagnosed 2 years before the emergence of hemiparesis; in case 2, diabetes insipidus developed 8 months after the onset of muscle weakness in the extremities; in cases 3 and 4, diabetes insipidus was absent. The presence of diabetes insipidus and the loss of other pituitary functions in the first two cases suggested germinoma, despite the atypical tumor localization.

The literature describes cases of the disease manifestation in the form of pathological hiccup and vomiting without hydrocephalus [10]. The cause of these symptoms is difficult to explain. Perhaps, they are related to hidden dissemination of the tumor to the medulla oblongata.

Figure 9. a — a histological specimen of germinoma, hematoxylin and eosin staining, magnification of 200x. The arrow indicates a syncytiotrophoblast multinucleated cell; b — immunohistochemistry with chorionic gonadotropin, magnification of 200x.
Also, the disease often manifests as mental disorders [13, 14]. Three of our patients had psychopathological symptoms in the form of disinhibition, foolishness, reduced self-criticism, and euphoria. These symptoms are probably caused by lesions of the thalamic nuclei and their connections to the frontal lobes.

According to the literature, basal ganglia germinomas are characterized by a diversity of MRI signs [8, 9, 14, 15]. Ji Hoon Phi et al. identified, based on 17 cases and literature data, 4 types of MRI patterns for growth of basal ganglia germinomas — from small areas with a changed signal in the basal ganglia projection, not accumulating a contrast agent, which are often interpreted as non-neoplastic lesions (stroke, demyelination), to large space-occupying lesions with strong contrast agent uptake and a pronounced mass effect [10]. Our observations fully confirm these data. There were also reported cases of multifocal germinomas involving the basal ganglia and other brain regions [9, 16—18]. A similar case was in one of our observations. Bilateral tumor growth may indicate ependymal spread of germinoma to the contralateral side and can help in the differential diagnosis from glial tumors.

According to the MRI data [15, 19, 20], basal ganglia germinomas are also characterized by atrophic changes in the brain at the lesion site. In this connection, it should be noted that a series of repeated brain MRI in one of our cases revealed a reduction in the basal ganglia lesion size with time, with a subsequent substantial lesion increase. The reason for this phenomenon was not clear because the patient did not receive hormone therapy that could facilitate edema reduction and partial regression of neurological symptoms. We did not find similar cases in the literature.

Because of a variety of the neuroradiologic signs of basal ganglia germinomas, examination of tumor metabolism using PET with C11-methionine can help in the differential diagnosis [7, 10, 21, 22].

Surgical treatment of basal ganglia germinomas is limited to stereotactic biopsy. In two of our cases, direct neurosurgical intervention was performed in association with a serious condition of patients caused by a severe mass effect and occlusion of CSF pathways. In case 3, right tumor resection led to worsening of left-sided hemiparesis, while right hemiparesis substantially regressed due to chemotherapy. In case 4, hemiparesis regressed in the postoperative period.

There are few publications on long-term treatment outcomes in basal ganglia germinomas [9, 10].

According to the data given therein, survival of patients was somewhat lower than that of patients with germinomas located along the midline. In 2010, Ji Hoon Phi reported a disease-free survival of 66% and overall survival of 77% in a series of 17 patients [10]. Y. Sonoda (2008) observed 3 tumor recurrences and 1 death in a group of 10 patients [9]. A possible cause for an unfavorable outcome is a late diagnosis of basal ganglia germinomas when the disease acquires a disseminated form, with the spread through the ventricular ependyma and subarachnoid spaces of the CNS. Also, a cause for recurrence may be an insufficient area of radiation therapy, which should involve the entire ventricular system in these cases [10, 17, 23, 24].

**Conclusions**

Basal ganglia germinoma is a very rare pathology. According to our experience and published data, basal ganglia germinomas are often diagnosed at a late stage due to atypical clinical symptoms and a variety of neuroradiologic signs. Establishing the diagnosis can be facilitated by disease manifestations in boys during the second decade of life; MRI signs of a bilateral basal ganglia lesion; neuroendocrine symptoms present in some of these patients despite the lack of MRI signs of a suprasellar lesion; psychopathological

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**Figure 10. Germinoma of the left thalamus.**

a — the tumor is large and heterogeneous and deforms the adjacent brain tissue and lateral ventricle; b — MRI 1 year after tumor resection and complex treatment. Postoperative changes in the anterior left thalamus are seen. A residual tumor is completely regressed.
Intracranial germ cell tumors (GCTs) account for 0.8—2.2% of all CNS tumors in children under 18 years of age. Germinomas occur 2 times more often than other GCTs. In 80% of cases, intracranial GCTs are localized in the pineal and suprasellar regions, which underlies clinical symptoms of the disease — endocrine disorders and hypertension symptoms. A basal ganglia localization of germinoma is rare, accounting for about 5% of intracranial germinomas.

The clinical picture of basal ganglia germinomas is represented by hemiparesis and extrapyramidal syndrome; mental disorders can occur.

A diagnostic method for germinomas, as well as for all CNS tumors, is MRI. Tumor markers AFP and HCG are not elevated in “pure” germinomas, and only syncytiotrophoblastic germinomas are characterized by a minor increase in the hCG level.

The MRI picture of basal ganglia germinomas is atypical and can miss tumor lesions.

Establishing the diagnosis of basal ganglia germinoma is a challenge for a common practitioner because of the rare tumor localization, absence of elevated tumor markers, and atypical clinical and MRI signs. The late diagnosis of germinoma is the cause for delayed treatment and, as a result, deterioration of treatment outcomes and persistence of neurologic symptoms. The article will be useful for practitioners because it describes the features of a clinical picture and neuroimaging classification and the prognosis. J of Neurology. 2010;109:227-236. doi: 10.1007/s00381-010-0119-7.

REFERENCES


O.G. Zheleudkova (Moscow, Russia)
A clinical case of combined treatment of a patient with breast cancer and metastases to the brain and meninges

E.A. MOSKVINA, D.R. NASKHLETASHVILI, A.KH. BEKYASHEV, S.V. MEDVEDEV, D.M. BELOV, T.G. GASPARYAN

Department of Oncological Neurosurgery, Blokhin Russian Cancer Research Center, Moscow, Russia

The article describes a clinical case of successful chemotherapeutic and radiation treatment of a patient with breast cancer and metastases to the brain and meninges and with a pronounced neurological deficit. The patient underwent combined treatment (whole brain radiation with TBD of 30 Gy and local radiation of a metastasis with TBD of 15 Gy associated with capcitabine therapy) with continued administration of capcitabine until improvement. A partial metastasis reduction by 50% and complete regression of the neurological deficit were observed. Disease-free period was 1 year and 10 months, and the overall survival amounted to 2 years.

Keywords: breast cancer, brain metastases, meningeal metastases, chemoradiotherapy.

Breast cancer is the most common oncological disease everywhere, including the developed countries [1]. In the structure of the incidence rate of malignant tumors in women, breast cancer takes the first place, and its ration is constantly increasing [2]. In 2006, the overall incidence of breast cancer in the countries of the European Union amounted to 109.8 cases per 100 thousand people a year, and the mortality rate from this pathology was 38.4 cases per 100 thousand people a year [1]. Metastatic breast cancer is considered to be an incurable disease [2] and still remains the leading cause of death from oncological diseases among European women [1]. Among malignances, breast cancer is the second in the frequency of brain metastasis occurrence (after lung cancer), which is 10-20% [3—6].

One of the most serious and severe complications of metastatic lesion of the central nervous system (CNS) is meningeal carcinomatosis, which is accompanied by severe neurological symptoms and associated with poor prognosis. Brain meninges serve a protective function providing liquor-haematinic, liquor-histological and histo-haematinic barriers. Lesions of CNS membranes are known to be revealed in approximately 7% of cancer patients. According to the autopsy data [7], the percentage of meningeal lesions is almost twice as high and equals 15-18%. In the structure of CNS membrane lesions, breast cancer is ranked third (8.5%) alongside with non-small cell lung cancer leaving small cell lung cancer (11-25%) and melanoma (23%) behind [8]. Therapy of the patients with CNS membrane lesions includes surgical treatment and chemoradiotherapy. Surgical treatment mainly involves installation of catheters and reservoirs for intrathecal administration of chemotherapeutic drugs or ventriculoperitoneal shunting in the case of hydrocephalus development [9]. According to some authors [10], analysis of the results of combined treatment of patients with meningeal carcinomatosis (chemoradiotherapy + intrathecal chemotherapy) showed that the median survival did not exceed 5 months. To date, the treatment of patients with brain lesion remains to be a major problem. Upon detection of metastases in the CNS, patients often do not receive further anti-tumor treatment, with a median survival without treatment amounting to not more than 1-3 months. There is no single standard for the treatment of metastatic brain lesions in breast cancer. Treatment in most cases is palliative and is aimed at improving the quality of the patient’s life [11].

A study of the efficiency of monochemotherapy with the drug capcitabine, as well as its combination with radiation therapy in disseminated breast cancer with metastases to the brain, including leptomeningal carcinomatosis, has been performed at the department of oncological neurosurgery of the ROSC named after N.N. Blokhin since 2008. The article presents a case of the successful application of combined (chemoradiation) therapy in a patient with metastatic lesion to the brain and meninges.

Patient P, 41 years of age, was diagnosed with breast cancer T2N0M0 in 2007. Since May 2007, the patient received preoperatively 3 courses of polychemotherapy according to the FAC scheme (500 mg/m² of fluorouracil intravenously on the 1st day, 50 mg/m² of doxorubicin intravenously on the 1st day, 500 mg/m² of cyclophosphamide intravenously on the 1st day; interval between courses was 3 weeks) with a moderate positive effect. Radical mastectomy was performed on the left side on June 4, 2007. The tumor was negative for estrogen receptors and weakly positive for progesterone receptors, Her2/neu status is unknown. A total of 3 courses of polychemotherapy were performed according to the FAC scheme after surgery. Hormone therapy was not administered. In July 2010, a severe headache occurred. Brain MRI with contrast detected metastases in the right occipital region, of parasagittal location, of about 6 cm in diameter, extending to the left occipital region in the form of a node of about 2.5 cm in diameter, with the involvement of the meninges of the tentorium of cerebellum and falx with a pronounced perifocal edema, compression of the posterior horn of the right lateral ventricle and displacement of midline structures 1.2 cm to the left (Fig. 1). The examination (X-ray of thoracic organs, ultrasound of abdominal cavity organs and retroperitoneal space, true pelvis, peripheral lymph nodes, skeletal scanning) revealed no metastases in other organs. The patient applied to the ROSC named after N.N. Blokhin. The patient's condition was estimated as moderate severity, did not progress. The severe neurological symptoms in the form of headache, dizziness, unsteadiness of gait, nausea, periodic vomiting, and double vision were noted. The patient received 16 mg of dexamethasone intramuscularly...
daily for 18 days with a moderate effect (headache intensity became slightly diminished).

Chemotherapy according to the scheme of 2,000 mg/m² of capecitabine per os daily for 14 days followed by a 7-day interval was prescribed to the patient. Radiation therapy to the entire brain with SBD of 3 Gy, TBD of 30 Gy and local radiation of metastasis with SBD of 5 Gy, TBD of 15 Gy were conducted simultaneously with the first two courses of capecitabine (from July 26 to August 12, 2010). Control examination was performed 1 month after the end of radiotherapy (after the 3⁰ course of capecitabine). The achieved effect was as follows: stabilization of the process, reduction in the maximum size of the lesion focus in the right parasagittal occipital region to 4.8 cm (20% reduction), reduction in the displacement of medial structures to 1 cm. Further, the patient received courses of monochemotherapy according to the scheme of 2000 mg/m² of capecitabine per os daily for 14 days followed by a 7-day interval. The patient received a total of 27 courses of capecitabine. There was no dose reduction. Control examination was performed after every 3 courses of chemotherapy. According to the data of brain MRI with contrast, a gradual increase in the positive effect was noted (reduction in the size of metastatic lesions in the brain, reduction in the displacement of midline structures), neurological symptoms were improved. Hematological toxicity was manifested mainly as neutropenia and reached the maximum of the II degree. Non-hematological toxicity was manifested as hand-foot syndrome of the I degree, increase in the levels of ALT, AST of the I degree. According to the control examination after the 24⁰ course of capecitabine (brain MRI with contrast, X-ray of the thoracic organs, ultrasound of abdominal cavity and retroperitoneal space, true pelvis, peripheral lymph nodes, skeletal scanning), partial effect of treatment has been noted: brain metastasis in the right occipital region decreased to 2.9 cm, the node spreading to the left occipital region was almost not visualizable, perifocal edema was not detected, the posterior horn of the right lateral ventricle was completely deployed, displacement of the midline structures to the left was 0.4 cm; there were no signs of metastases in other organs. The patient did not require

Figure 1. MRI of the brain with contrast prior to chemoradiotherapy.
glucocorticosteroid administration, the state was satisfactory, there were no neurological symptoms, pursued her profession.

The examination after the 27th course of capecitabine showed process stabilization in the brain (brain lesion remained the same size, 2.9 cm) (Fig. 2). However, the disease progression was noted: metastases in the spinal cord at T4—T5, T9—T11, and L3—L5 levels, there were no lesions of other organs. As a result, the disease-free period was 1 year and 10 months by May 2012. The patient received radiation therapy of lesions in the spinal cord. The patient's condition deteriorated rapidly, neurological symptoms increased (lower paraplegia, disturbance of pelvic organ functions, general weakness). The patient died in July 2012 as a result of the progressive process in the spinal cord. Overall survival was 2 years.

Advisability of treating breast cancer metastases in the brain is no longer questioned to date, despite its palliative nature, since it is possible to extend the life of individual patients for 2 years or more. Surgical treatment of metastatic lesion to the meninges is possible in cases of nodular dissemination around meninges upon the removal of the adjacent metastatic lesion. In the case of the sensitivity of primary tumor to chemoradiotherapy, the successful application of conservative methods of treatment is possible.

There is no conflict of interests.
This paper is devoted to one of the most serious and severe complications of breast cancer: metastases to the brain and meningeal carcinomatosis, which are accompanied by pronounced neurological symptoms and associated with poor prognosis.

The authors demonstrate a clinical case with long-term survival period in a patient with metastases to the brain and meningeal carcinomatosis using chemoradiotherapy with further maintenance therapy with capecitabine.

Combined application of radiotherapy and capecitabine resulted in a pronounced effect with rapid regression of neurological symptoms. Maintenance therapy with capecitabine provided long disease-free period with minimal side effects and high quality of the patient’s life. Convenience and long (two-week) course of capecitabine make it the drug of choice for radiosensitization. This approach to the treatment of breast cancer patients with metastatic lesions to the brain and its meninges requires further research in the prospective studies.

A.V. Golanov (Moscow, Russia)
Surgical Treatment of Clival and Axial Bone Cysts

A.N. SHKARUBO1, A.A. KULESHOV2, I.A. SEMENOVA3, L.V. SHISHKINA1, V.V. SHVETS1, M.S. VETRILE2, I.S. GROMOV2, V.V. MARSHAKOV2, I.V. CHERNOV2

1Burdenko Neurosurgical Institute, Moscow, Russia; 2Priorov Central Institute of Traumatology and Orthopedics, Moscow, Russia; 3Nasonova Research Institute of Rheumatology, Moscow, Russia; 4Sechenov First Moscow State Medical University, Moscow, Russia

Objective. The study objective is to present the tactics of surgical treatment of simple (solitary) bone cysts of the clival region and C2 vertebra. Material and methods. Two patients were operated on for simple clival and axial bone cysts. Results. The first patient with a simple cyst underwent transoral clivectomy and bone cyst evacuation. Postoperative control SCT scans revealed that the bone cyst was lined with hemostatic material and biological glue and bone structures of the clivos was restored in 8 months. The second patient with a simple cyst of the second cervical vertebra (axis) underwent a two-staged surgical treatment: first, occipitopetrospondylodesis was carried out, followed by transoral removal of the pathological process of C2 vertebral body as the second stage. Control scans a year after the surgery revealed formation of bone tissue in the axis body region, increased cystic cavity in the odontoid process of the axis, and posterior migration of the latter, which caused compression of the brainstem structures. In connection with this, we performed transoral re-intervention with removal of separated cystic odontoid process. Postoperative control scans revealed complete removal of cystic odontoid process and decompression of the dural sac. The article provides the detailed analysis of the modern world literature. We found no reported cases of the simple bone cyst located in the clivos or superior cervical vertebrae and, therefore, no described tactics for surgical treatment of these complex diseases. This article presents illustrative preoperative, intraoperative, and postoperative images and histological preparations. Conclusion. We report cases of successful recurrence-free surgical treatment of simple (solitary) bone cysts located in the clivos region (1st case) and in the body and odontoid process of the axis (2nd case). The second case was peculiar in that the patient had an extremely rare combination of the bone cyst of C2 vertebral body and separated cystic odontoid process of the axis (cystic os odontoideum).

Keywords: transoral approach, simple clival cyst, simple C2 cyst.

Bone cyst (solitary, simple, juvenile, isolated, dystrophic) (M 85.4) is a tumor-like lesion of various skeletal bones in the form of a monolocular cavity filled with clear or slightly bloody contents and internally lined with connective tissue of varying thickness with giant multinucleated osteoclasts [1—3]. Researchers have no single viewpoint with regard to bone cyst pathogenesis [4]. In particular, T.P. Vinogradova [4] considered bone cyst as a developmental stage of osteoblastoma. I.G. Lagunova [5] in 1962, and S.A Rheinberg in 1964 [6] regarded this pathology as a local dystrophic process accompanied by cystic bone degeneration. According to A.P. Berezhnoy and other authors [7, 8], bone cyst is a reactive pathological condition, which arises in the bone growth area due to intraosseous homeostasis disorders with impaired microcirculation of arteriovenous shunts and development of high intraosseous pressure. S.T. Zatsepin [9] suggested that the development of bone cyst result from dysplasia of an area of the bone growth plate accompanied by the development of vascular changes.

Simple bone cyst accounts for 3% of all bone lesions [7, 10]. In 85% of cases, local solitary lesions occurs in children and adolescents in the first two decades of life, usually between the ages of 8 to 14 years. In adults, bone cysts are less common. Bone cyst is 2 times less common in girls than in boys [4, 10].

Proximal metaphyses of the humerus, femur, andibia (90—95%) are the most common cyst sites. They are much less frequently located in the diaphysis (12.4%) [3, 4, 10]. Cysts can be found in other bones: the pelvis, skull, shoulder blades, ribs, jaw, and calcaneus. Cysts of the femur and humerus are typical of patients under 20 years. In elderly patients, they can develop in the iliac and heel bones. There are case reports, where bone cysts were located in the spine [11—27]. In the available world literature, we found no cases of simple cyst located in the clivos or superior cervical vertebrae.

Case 1

Eight-year-old girl was admitted to the Neurosurgical Institute on 22.02.08 with a paroxysmal meningeal-like headache, which was first noted by the patient in September 2007. Since December 2007, the pain was accompanied by vomiting. MRI was performed by the place of residence and clivos tumor was detected. Examination conducted at the Neurosurgical Institute revealed no focal symptoms. CT study showed that bone structure of the clivos is “spare” with preserved cortical layer and sphenoidal synchondrosis. MRI study in the clivos projection detected space-occupying mass; the intensity of the signal from this mass was homogeneously increased in T2 mode and low in T1 mode (Fig. 1).

Transoral trepanation of the clivos with bone cyst evacuation was carried out. We performed skeletonization of the anterior half-ring of C1 vertebrae, the medial and inferior parts of the clivos. The clivos was “swollen”. Its anterior portions significantly bulged in the anterior direction (compared to the conventional arrangement of the clivos). Trepanation of the anterior parts of the clivos was carried out using high-speed drill. Clear liquid leaked from the resulting bone defect under pressure. Additional trepanation of the superior portions of the clivos was carried out. Bone bridges and soft tissue lining of the cavity were observed, which were removed and sampled for analysis. After cyst evacuation, the cavity was continuously filled with a clear, colorless liquid, cerebrospinal fluid. Cyst cavity was first examined using 0° endoscope and then 30° endoscope. Examination with 30° rigid endoscope detected fistula in the right superior segments of the clivos, through
which cerebrospinal fluid leaked from the basal cisterns. Thorough endoscopic inspection was carried out and no tumors were found. Fistula area was lined with hemostatic material. Liquorrhea stopped. In addition, clivus trepanation area was sealed with biological two-component fibrin-thrombin glue. The pharynx was closed in layers. Soft palate was sutured. At the end of the operation, gastric tube was placed.

Morphological study showed that the material mostly consist of compact bone fragments (sometimes thinned) and scattered spongy bone trabeculae having plate-like structure. Bone trabeculae were irregularly calcified. Some compact bone fragments included small spaces filled with spongy fibrous tissue. We observed scattered bony structures of cyst cavity, which were internally lined with a layer of fibrous tissue having varying thickness. Cyst lining contained a few multinucleated giant osteoclasts. There was mild focal cholesterosis. Separate structures of cyst lining were detected (Fig. 2). Based on the above, final diagnosis was established as bone cyst of the clivus.

At the time of discharge, the child had no headache. There were no signs of oral and nasal liquorrhea.

Control radiograph 8 months after the surgery showed complete regression of the fistula and partial recovery of bone structures in the clivus (Fig. 4).

Control radiograph 20 months after the surgery showed further recovery of bone tissue in the clival area. (Fig. 5).

Control radiograph 5.5 years after the surgery showed cyst obturation, almost completely restored bone structure of the clivus, as well as restored external and internal cortical plates of the clivus (Fig. 6).

Case 2

Fourteen-year-old boy was admitted to N.N. Priorov CITO on 30.04.08 suffering from the pain in the cervical spine, movement restraints, and forced head tilt.

Case history shows that the patient experienced weakness in his arms and legs and pelvic disorders after sharp bending of the cervical spine during a game on 15.01.08. CT and MRI were performed according to the place of residence. The patient was diagnosed with contusion of the cervical cord and tetraparesis accompanied by delay-type pelvic disorders.

CT and MRI examination at the CITO revealed malformation of the superior cervical spine, cyst (aneurysmal?) of C2 vertebral body and “odontoid bone” of C2 vertebra, and nonclosure of the anterior half-ring of C1 vertebra (Fig. 7).

Neurological status was characterized by tetrapyramidal insufficiency in the form of mild spastic increase in muscle tone and high tendon reflexes with extended zone, pathological hand and foot reflexes. The strength in hands and feet was 4 points.

Figure 1. Case 1.

a — preoperative spiral computed tomography (CT); b — T1 MRI; c — T2 MRI (described in text).

Yellow arrow indicates fistula. Red arrows indicate clival cyst. Green arrows indicate the sphenoidal sinus.
The patient underwent two-stage surgery (operations were carried out at the CITO by the cooperative group of CITO and Neurosurgical Institute staff). First, occipitospondylodesis was carried out. Control postoperative X-ray radiography of the head and cervical spine confirmed the correct state of the stabilizing system (Fig. 8).

Postoperative period was uneventful. No negative dynamics of neurological status was observed, but the original reduction in the strength of hands and feet to 4 points persisted.

In 38 days, the second stage of surgical treatment was carried out: transoral removal of the lesion of C2 vertebral body. Skeletizing of C2 body and the lower edge of C1 arch using a high-speed pneumatic drill was followed by trepanation of the cortical plate of C2 vertebra. The cyst was evacuated under pressure (xanthochromic liquid). Burr window was extended to 14x14 mm. Bony bridges and soft tissue lining of the cavity were observed, which were removed and sampled for analysis. Cyst cavity was tightly filled by 1/3 with biocomposite osteoplastic material, stimulating bone formation, and by 2/3 with bone autograft taken from the area of the right iliac wing.

Postoperative period was uneventful. The neurological status was characterized by regression of pyramidal insufficiency (5 points on both sides).

Morphological study of the material revealed scattered spongy bone trabecula having plate-like structure, small fragments of fibrous tissue, red blood cells, and single cells of hematopoietic bone marrow. Bone trabeculae are thin and some of them are irregularly mineralized. Histologic pattern based on clinical and x-ray data was consistent with solitary (simple), rather than aneurysmal bone cyst (Fig. 9). Follow-up examination 1 year after the surgery revealed formation of bone tissue at C2 vertebral body, increases cystic cavity in the odontoid process of the axis, and its posterior migration, causing compression of the brainstem structures (Fig. 10).

In this regard, transoral removal of the “odontoid bone” of C2 vertebra (separated odontoid process of the axis) was performed. Dissection of the throat was followed by skeletization of C2 vertebral body and C1 arch, which was resected. The walls of the odontoid process were severely thinned. Cyst evacuation was accompanied by outflow of pressurized xanthochromic liquid. Separated odontoid process of C2 vertebra was isolated. Odontoid process of the axis was fragmented using high-speed pneumatic drills and pistol osteotribe and completely removed (Fig. 11). The dura mater was not damaged. There were no intraoperative liquorrhea. The wound was sutured in layers.

Postoperative period was uneventful. Morphological study revealed scattered osseous trabecula with cyst lining structures in the form of the thin strip of fibrous tissue with elongated fibroblasts. Thus, the morphological picture also corresponded to solitary (simple), rather than aneurysmal bone cyst (Fig. 12).

Follow-up examination 7 days after the surgery showed complete removal of the cystic “odontoid bone” and dural sac decompression (Fig. 13).

**Discussion**

Solitary bone cysts are extremely rare in spinal bones. Despite the fact that they are caused by unknown reasons, some mechanisms of their formation have been studied, such as venous obstruction, trauma, and lymphatic drainage disorders [28, 29].

**Clinical features**

Bone cysts are characterized by pain, swelling in the involved area, and sensation of discomfort. Cysts are often asymptomatic. In 75% of cases, bone cyst manifests as
pathological fracture caused by even minor injury. The disease develops slowly and may proceed for many years [3, 4, 30—33].

**Radiodiagnosis**

According to clinical and radiological presentation, solitary bone cysts are divided into active and passive ones [4, 7, 8]. X-ray picture of bone cyst represents a focus of lytic destruction [3, 4, 10]. In the long bones of young children, it is located in the central portion, while in older children, it is located in eccentric parts and has smooth, well-rounded contours. The cortical layer is thinned, moderately “swollen”, but its integrity is not compromised. If there is no pathological fracture, periosteal reaction is absent.

Magnetic resonance imaging confirmed the presence of the liquid contents in the cyst cavity and blood in the area of pathological fracture.

The computed tomography and magnetic resonance imaging are the most advisable methods in the case of pathological process located in the spinal, pelvic, and cranial bones. [10]
Figure 6. Case 1.

a — MRI; b — SCT 5.5 years after the surgery (described in text).
Red arrows indicate almost completely recovered bone structures of the clivus. Green arrow indicates the cavity of the sphenoidal sinus.

Figure 7. Case 2.

a — MRI; b — preoperative CT. Cyst (aneurysmal?) of the body and odontoid process of C2 vertebra.
Green arrows indicate separated odontoid process of C2 vertebra (so-called “odontoid bone”).
Yellow arrows indicate the cyst of C2 body. Orange arrow indicates intramedullary cyst at C2 level. Red arrow indicates the cleft of the anterior half-ring of C1 vertebra.
Figure 8. Case 2. XRD pattern after the first phase of surgical treatment (occipitopondylodesis).

Figure 9. Case 2. Histological preparation. C2 body cyst.
1 — bone; 2 — connective-tissue lining of the cyst; 3 — multinucleated giant cell.
Hematoxylin & Eosin stain x 200.

Figure 10. Case 2
a — SCT; b — 3D SCT; c — MRI (T1, T2) 1 year after the surgery (described in the text).
Green arrows indicate the growth of the cystic cavity in the odontoid process of the axis and its posterior migration. Yellow arrows indicate formation of bone tissue in the area of C2 vertebral body.

Morphological characteristics
Bone cyst puncture results in discharge of yellow liquid. Macroscopic view of bone cyst shows a cavity with minimal amount of light yellow or yellow-pink clear serous liquid contents. Microscopic view of the cyst shows smooth inner wall. Cyst lining is barely distinguishable and contains fibroblasts, histiocytes, and isolated multinucleated giant osteoclasts. Lining is often rich in thin-walled, dilated vessels. Hemosiderin deposits, scarce foam cells, cholesterosis foci, and reactive osseous trabeculae can be observed. Cyst wall can
contain fibrin-like masses, hyalinized or calcified areas [3, 13]. In the case of pathological fracture, osteochondral callus elements are observed [4, 13, 31, 34]. Morphological differential diagnosis with the aneurysmal bone cyst, parathyroid osteodystrophy, giant cell tumor, nonosteogenic fibroma, and fibrous dysplasia should be done [2-4, 31, 32, 34].

**Genetics**

There are scares genetic studies in the literature. It was previously reported that the complex of clonal structural rearrangements involves 4, 6, 8, 16, 21 and both 12th chromosomes [28]. In later works, translocation t (16; 20) (r11.2; q13) was observed in one case. In another case, complex karyotype anomaly was reported, where late relapse demonstrated TP 53 mutation [3].

**Treatment and prognosis**

Currently, there are numerous treatments of bone cysts. Prosthetic procedure includes long-term immobilization of the injured area with 50% cure rate. Conservative treatment includes drainage of the cyst cavity followed by administration of various drugs affecting cyst contents and lining. Puncture under CT control involves the removal of cyst contents, wall perforation for cavity drainage followed by administration of the mixture consisting of demineralized bone meal and fresh blood. [35] Surgical treatment includes resection of the pathological focus with plastic repair of the defect [36].

According to the results of meta-analysis conducted by Muayad Kadhim et al. [37], in 77.4% of cases, bone cysts can be cured by injecting methylprednisolone acetate, which is comparable with the results of bone marrow injection into the cyst cavity (77.9%). Surgical treatment using both autograft and allograft results in recovery in 90% of cases.
In the active stage, surgery is inappropriate, since lysis processes prevail over the repair processes, which results in graft resorption and formation of residual cavities [7, 8, 38] and relapses occur in 10–20% of cases [3, 4, 31, 34].

In the available world literature, we found no descriptions of cases of simple (solitary) cyst located in the clival and superior cervical area.

However, the literature describes cases of aneurysmal cysts involving either separate Cl vertebra (4 cases), or separate clivus (2) [39–43].

Conclusion

We report cases of successful relapse-free surgical treatment of simple (solitary) bone cyst located in the clival area, as well as in the area of the body and the odontoid process of the axis. The characteristic feature of the second observation was that the patient had an extremely rare combination of bone cysts of the body and “separated” cystic odontoid process of C2 vertebra (“odontoid bone”).

There is no conflict of interests.

REFERENCES

Commentary

The article presents detailed report of two clinical cases of bone cysts of the clivus and axis. Undoubtedly, the work is of high scientific and practical interest, all the more so, as clinical cases of bone cysts located at the skull base and craniovertebral junction were not previously reported in the literature.

These cases are rare and very interesting from the clinician’s point of view, which makes them very illustrative. In addition, the authors demonstrated perfectly executed operations. I believe that this work should be published in “Problems of neurosurgery” journal, since it is novel and provides information, which is useful for colleagues.

A.O. Gushcha (Moscow, Russia)

Commentary

The information provided in this article is fundamentally novel. The work is well structured, illustrated, and argued. The authors are advised to clarify once again the details of separate cystic lesions of the odontoid bone and C2 vertebral body, demonstrating characteristic features of cyst embryobiogenesis in conclusion. These technical details will improve the perception of the article by its readers.

Undoubtedly, the article is of practical interest and can be recommended for publication in a specialized neurosurgical journal.

A.Yu. Mushkin (St. Petersburg, Russia)
Guidelines for the Diagnosis and Treatment of Severe Traumatic Brain Injury. Part 2. Intensive Care and Neuromonitoring

A.A. POTAPOV¹, V.V. KRYLOV², A.G. GAVRILOV², A.D. KRAVCHUK¹, L.B. LIKHTERMAN¹, S.S. PETRIKOV², A.E. TALYPOV², N.E. ZAHKAROVA³, A.V. OSHOROV¹, A.A. SYCHEV¹, E.V. ALEXANDROVA¹, A.A. SOLODOV²

¹Burdenko Neurosurgical Institute, Moscow, Russia; ²Skilfosovsky Research Institute of Emergency Medicine, Moscow, Russia

3. Intensive care and neuromonitoring of the patients with severe TBI

Basic life support is needed: recovery and support of respiration (restoration of airway patency and correction of hypoventilation disorders, such as hypoxemia and hypercapnia) and blood flow (correction of hypovolemia, hypotension and anemia) (standard care).

3.1 Monitoring (guidelines)

Rational intensive care needs to be based on monitoring vital functions. Neuromonitoring, monitoring of blood flow, respiration, arterial and cerebral oxygen saturation should be performed in patients with suppressed wakefulness (GCS score ≤8). The optimal measures include continuous monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP), monitoring of cerebral oxygen saturation (measuring brain tissue oxygen tension, cerebral oximetry in the par-infrared range, or measuring hemoglobin oxygen saturation in the jugular vein bulb through a catheter placed retrograde), monitoring arterial pressure (invasive procedure is preferred), pulse oximetry, monitoring carbon dioxide concentration in respiratory gas and heart rate.

Where possible, these primary diagnostic measures should be expanded by ultrasonography of the cerebral vessels, monitoring central venous pressure, systemic hemodynamics, evaluation of the acid–base balance of arterial and venous blood, and tissue microdialysis [1—9].

3.2. Respiratory support

Patients with disorders of awakening (GCS score ≤10, soporose and comatose state) require tracheal intubation and respiratory support to prevent aspiration complications and ensure normal oxygen saturation of arterial blood and correct hypercapnia (standard care).

The trachea should be intubated with minimum flexion or extension of the cervical spine: (either nasotracheal intubation or orotracheal intubation with the spinal axis maintained). In case of a soporose or comatose state, patients undergo assisted or volume-controlled ventilation with an oxygen–air mixture with oxygen content of at least 40—50%. Proper selection of ventilation modes or the use of short-acting muscle relaxants and sedatives is required to prevent the episodes of non-synchronism between the respirator and the patient’s respiratory attempts during ventilation, which abruptly increase ICP. PaCO₂ needs to be maintained at 36—40 mm Hg and oxygen hemoglobin saturation in blood outflowing from the brain, at ≥60%. To prevent cerebral hypoxia, all the manipulations related to interruption of the contour of the medical ventilation apparatus need to involve pre- and post-oxygenation with 100% oxygen. Hyperventilation and hyperventilation-induced hypocapnia should be prevented during mechanical ventilation. Long-term hyperventilation (PaCO₂ <30 mm Hg) has to be avoided during the first 5 days if patients with severe TBI show no signs of intracranial hypertension (standard care).

Preventive hyperventilation (PaCO₂ <35 mm Hg) during the first 24 h after injury should also be avoided because there is a risk of worsening of cerebral perfusion during the period of reduced volumetric cerebral blood flow (recommendations).

Short-term hyperventilation can be used in case of sudden worsening of the neurological status or during a longer time if intracranial hypertension persists despite using the sedatives, muscle relaxants, CSF drainage from cerebral ventricles, and the use of hyperosmolar solutions. If hyperventilation is used in patients with PaCO₂ <30 mm Hg, oxygen hemoglobin saturation should be measured in the jugular vein bulb, the arteriovenous oxygen difference should be determined and/or oxygen tension in cerebral tissue should be evaluated [1, 6, 10—13] (options).

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3.3. Correction of arterial hypotension (recommendations)

The CPP value needs to be maintained at a level of at least 60 mm Hg in order to correct cerebral perfusion disorders. At all the stages of rendering medical aid (at the injury site, during transportation, and under inpatient treatment), arterial hypotension (systolic blood pressure <90 mm Hg) needs to be immediately and meticulously prevented or corrected. Mean blood pressure should be maintained above 90 mm Hg during the whole duration of intensive care. Severe TBI is one of the few pathologies when arterial hypotension requires administration of sympathomimetic agents parallel to infusion therapy to increase CPP. Today, there are no convincing literature data demonstrating that a certain sympathomimetic agent is superior to other ones. Depending on the state of systemic hemodynamics and the clinical presentation, long-term intravenous infusion is used: noradrenaline (0.01—3 µg/kg/min), dopamine (1—2 µg/kg/min — affects D-receptors, usually stimulates urine production, 2—10 µg/kg/min — also affects β-receptors and increases cardiac output, >10 µg/kg/min — additionally affects α1-receptors and causes vasoconstriction), mesatone (0.4—5 µg/kg/min), and in rare cases, dobutamine (0.5—20 µg/kg/min). Infusion of colloid and crystalloid solutions should be performed in case of hypovolemia. Osmolarity and plasma sodium concentration need to be monitored. Low osmolarity (<280 mOsm/L) and sodium concentration (<135 mmol/L) are corrected towards higher values. Hyposmotic solutions (e.g., 5% glucose solution) are not used in therapy of acute TBI [1, 6, 7, 8, 9, 14].

3.4. ICP monitoring

ICP monitoring is indicated for patients with severe TBI (GCS score < 8) and a pathology proved by CT scanning (hematoma, contusion focus, edema, or compressed basal cisterns). It is reasonable to monitor ICP in comatose patients showing no pathological alterations in CT scans and having one of the following characteristics: over 40 years old, unilateral or bilateral decerebration, systolic blood pressure <90 mm Hg. Measuring ventricular pressure is the most accurate and reliable ICP monitoring method. This procedure also allows one to remove cerebrospinal fluid (CSF) in therapeutic purpose [6—9, 14, 21] (recommendations).

Kocher’s point at the subdominant hemisphere is the preferred site for inserting an external ventricular drain. When the dominant hemisphere cannot be identified, the drain is preferably placed on the right site at Kocher’s point [20] (options).

Before the drain is installed, the entire system should be filled with sterile normal saline. This manipulation needs to be performed by two physicians: a surgeon who directly places the drain and his/her assistant who helps to maintain sterile conditions [20] (options).

Special care is needed when performing external ventricular drainage in patients who have a subtentorial mass effect because of the risk of developing paradoxical dislocation due to the emergence of a pressure gradient and in patients with the mass effect of contralateral drainage because of the risk of dislocation worsening [20] (standard care).

In case of sanitation of the tracheobranchial tree or using a purgative enema, the external ventricular drainage needs to be temporarily closed to prevent undesired hyperdrainage. Sedation is recommended in patients with external ventricular drainage before these procedures [20] (options).

If intrahospital transport of patients with external ventricular drainage is needed, the drainage should be closed during the manipulation to prevent hyperdrainage [20] (options).

To prevent errors by medical personnel during intravenous administration of medications, the external ventricular drainage port needs to be clear marked in a way differing from that used for the intravascular insertion ports [20] (options).

ICP monitoring using a sensor inserted intraparenchymally is commonly used in clinical practice for patients with severe TBI, since it is difficult to make a ventricular puncture to measure the intraventricular pressure for the ventricular system narrowed and displaced.

3.5. Indications for correction of ICP

Correction of ICP should be started at ICP values higher than the threshold of 20 mm Hg registered for 5 min and longer [6—9, 14, 21] (recommendations).

3.6. CPP monitoring and the optimal CPP levels

In the daily intensive care routine, maintenance of CPP in patients with cerebral edema is ensured by moderate arterial hypertension using catecholamines and infusion solutions. The desired CPP values lie within the range of 50—70 mm Hg. A short-term increase in CPP may occur in patients with intact autoregulation of the cerebral blood flow without any significant aggravation of the injury outcomes. Auxiliary monitoring of the cerebral blood flow, oxygen saturation, and metabolism makes it easier to choose the optimal CPP parameters.

Aggressive attempts to maintain cerebral perfusion pressure above 70 mm Hg using infusion therapy and catecholamines should be avoided because of the risk of developing edema and acute pulmonary lesion (recommendations).

The CPP value below 50 mm Hg should be prevented (options).

3.7. Monitoring of autoregulation of cerebral blood flow (options)

The use of induced arterial hypertension in patients with disturbed autoregulation of the cerebral blood flow is fraught with intracerebral complications: blood—brain barrier disturbance, development of vasogenic cerebral edema and induced intracerebral hypertension. Development of extracerebral complications during CPP-oriented therapy, such as myocardial dysfunction and pulmonary lesion accompanied by development of edema and acute pulmonary lesion has been confirmed. These complications significantly increase the mortality among TBI patients and counterbalance the initial efficacy of the CPP protocol [7]. The therapeutic strategy aimed at maintaining CPP is an aggressive method of intensive care: some authors believe [22] that it should be focused on the status of autoregulation of cerebral blood vessels. Monitoring the pressure reactivity index (PRx) is one of the reliable and safe methods for continuous assessment of autoregulation of cerebral vessels [22]. The method does not require any function tests and is based on analyzing wave-like fluctuations in blood pressure and ICP. Furthermore, the method allows one to calculate the optimal CPP, providing a
landmark for targeted CPP therapy [22]. The optimal CPP value should correlate with the minimal PRx value.

### 3.8. Treatment of intracranial hypertension

Therapy of intracranial hypertension is classified into background (preventive) and urgent therapy.

#### 3.8.1. Background (preventive) therapy

Preventive measures to correct intracranial pressure above 20 mm Hg prove inefficient, the stepwise algorithm for reducing ICP is used.

##### 3.8.2.1. CT of the brain is performed to rule out the reasons for intracranial hypertension requiring surgical correction (standard care).

##### 3.8.2.2. If an intraventricular catheter was inserted, controlled CSF drainage is used. An absolute indication for controlled drainage of CSF is intracranial hypertension caused by disturbed CSF flow in patients with occlusive hydrocephalus (standard care).

##### 3.8.2.3. Hyperosmotic solutions in treating intracranial hypertension

The use of hyperosmotic solutions is the most common methods for nonsurgical correction of intracranial hypertension. Nowadays, 15% mannitol solution is most often used in Russia. Bolus injections of mannitol at a dose of 0.25—1.0 g per kilogram body weight are used. The daily dose of administered mannitol should not be higher than 140—180 g. It is reasonable to administer mannitol before ICP monitoring if a patient has signs of trautentorial herniation or neurologic worsening unrelated to extracranial factors [1, 6, 7, 21, 25] (recommendations).

The osmolality of blood plasma needs to be constantly monitored when using hyperosmotic solutions and the therapy should be stopped once the osmolarity of 320 mOsm/L is reached.

Acute kidney failure is a complication of the therapy using hyperosmotic solutions. The risk of developing acute kidney failure rises when plasma osmolality increases to 320 mOsm/L and above and/or at hypernatremia >160 mmol/L [26, 27]. In patients with cardiopulmonary disorders, hyperosmolar therapy may cause the overload of the lesser circulation and pulmonary edema; rapid administration of hyperosmotic agents may be accompanied by arterial hypotension because of reflex transient decrease in the total peripheral resistance. Mannitol-induced osmotic diuresis may also contribute to arterial hypotension, especially in patients initially presenting with hypovolemia. When using mannitol, intracranial pressure can even increase above the original level after the initial decrease (the so-called rebound effect) [28, 29]. The development of the rebound effect is attributed to the delayed change between the osmolarities of blood plasma and the cerebral interstitial space [29]. A serious complication of using hypertonic sodium chloride solution in patients with the initial chronic hyponatremia is central pontine myelinolysis (rapid movement of fluid from the pontine cells into the vascular bed caused by hyperosmolality of blood plasma). Hypertonic solutions must be administered very slowly to prevent this condition in patients with chronic hyponatremia.

The use of barbiturates in treating intracranial hypertension

Therapeutic anesthesia with high-dose barbiturates can be used in patients with severe TBI with stable hemodynamics and intracranial hypertension resistant to the maximally aggressive conservative and surgical treatment methods [1, 6, 7] (recommendations).

When using therapeutic anesthesia with barbiturates, it is reasonable to control the arteriovenous oxygen difference, since there is a risk of developing cerebral oligemic hypoxia (options).

The drug at a dose of 10 mg/kg during 1 h is initially administered followed by infusion of 3 doses (5 µg/kg during 1 h) and maintaining the achieved plasma barbiturate concentration using an automated infusion pump (1 mg/kg during 1 h). Monitoring of sedation depth and choosing the optimal drug dose to suppress cerebral metabolism should be performed by electroencephalography or BIS monitoring.

Artificial hypothermia in treating intracranial hypertension

Moderate reduction of brain temperature suppresses cerebral metabolism, which in turn may reduce cerebral blood flow, intracranial blood volume, and ICP. Moderate hypothermia modes (up to 32—35°C) are used [1, 6, 7, 14, 30, 31].

Cooling of the patient to the required temperature should be performed quickly (within 30—60 min), while heating should be slow (0.2—0.3°C within 1 h). Cooling of the patient can be accompanied by serious complications: hypocoagulation, increased diuresis, electrolyte imbalance, insufficient moistening of the incoming air, and infectious complications (options). The possible adverse effects of hypothermia are most typical of uncontrolled and deep hypothermia (patient’s body temperature less than 30°C).

The use of hyperventilation in treating intracranial hypertension

Hyperventilation is a temporary measure for reducing increased intracranial pressure (e.g., when a patient is transported to the operating room if all the conservative measures for correcting intracranial hypertension proved inefficient). When using hyperventilation, one should monitor whether oxygen supply to the brain is sufficient by measuring blood oxygen saturation in the jugular vein.

\( SV_O_2 \) indices lying within 55—75% are considered normal, provided that oxygenation of arterial blood is sufficient. The normal \( PhbO_2 \) is 25—35 mm Hg at oxygen tension in the arterial blood of 80—100 mm Hg [1, 6, 7] (recommendations).

Hyperventilation can be an efficient method for correcting
intracranial hypertension caused by cerebral hyperemia [18, 32].

3.9. Role of glucocorticoids in the acute phase of severe TBI

Since 2000, the use of glucocorticoids to treat the acute phase of severe TBI has not been recommended, since according to the results of a number of class I and II studies, these agents do not reduce ICP and do not improve the outcome in patients with severe TBI (standard care). A randomized study carried out in 2004 in patients with severe TBI (CRASH) showed higher mortality among the patients who received high-dose methylprednisolone compared to those who received placebo. A meta-analysis published by the Cochrane Community shows that the patients had an increased risk of gastrointestinal bleeding after receiving glucocorticoid therapy.

The use of glucocorticoids is reasonable in patients with diencephalic damage and hormonal insufficiency caused by it.

3.10. Infectious complications in patients with severe TBI

3.10.1. Prevention and treatment of pulmonary complications

3.10.1.1. Prevention of aspiration of the oropharyngeal and gastric contents

Early tracheal intubation and maintaining the required pressure (20–25 cm H2O) in endotracheal tube cuffs is required. Continuous supra-cuff suction is used to prevent pulmonary aspiration. Tracheostomy is needed for mechanical ventilation lasting more than 5 days [10] (standard care).

To prevent gastroesophageal reflux, the patient should be positioned to his/her side on the bed with the head end elevated and receive enteral feeding through a nasojejunal tube (standard care). At late stages of treating severe TBI, percutaneous endoscopic gastrostomy can be performed in patients with signs of dysphagia (recommendations).

3.10.1.2. Prevention of cross-contamination and colonization through personnel hands (recommendations)

Mechanical ventilation equipment and fibrobronchoscopes should be meticulously cleaned; regular monitoring of bacteriological contamination of mechanical ventilators after sterilization should be performed. The order of individual use of aspiration equipment should be maintained and repeated use of sanitization catheters should be prevented. If possible, specialized closed systems for sanitation of the tracheobronchial tree and combination breathing filters should be used. A person performing sanitation of the tracheobronchial tree needs to wear sterile gloves. After any manipulations with the patient, one should wash his/her hands and gloves with special alcohol-based disinfectants. Hands should be washed with running water and dried with disposable paper towels or napkins.

When prescribing antibacterial therapy, one should take into account the pharmacokinetic properties of antibiotic drugs, choose dosage with allowance for the minimally suppressive concentrations, and perform scheduled drug rotation [1].

3.10.2. Prevention and treatment of intracranial suppurative complications

Antimicrobial prophylaxis that takes into account the microbiological status of the inpatient unit is indicated for scheduled and emergency neurosurgical interventions.

Failure to comply with the aseptic/antiseptic rules when manipulating the external ventricular drainage is the most common cause of intracranial infection. The risk of developing intracranial pyoinflammatory complications increases during long-term external CSF drainage [20] (recommendations). CSF drainage for more than 14 days is associated with the high risk of developing intracranial infection.

To reduce the risk of intracranial pyoinflammatory complications during external CSF drainage, the medical personnel needs to be trained to handle the drainage system and collect biological samples for analysis. Routine replacement of any elements of the drainage system should be avoided unless absolutely necessary. The system needs to remain closed as well as air- and watertight during the entire duration of CSF drainage. CSF can be collected for the analysis only through a special port that prevents system’s unscrewing and detachment of the pieces. If accidental detachment of any elements of the system occurs, all the elements connected to the external ventricular drainage system need to be replaced. Samples can be collected from the drainage system only when strictly adhering to the aseptic and antiseptic techniques. Before sample collection, it is recommended that the sample port is treated with solutions of mono- and polybasic alcohols (e.g., 70% ethanol solution, chlorhexidine/ethanol solution) for 3 min that are allowed to be used for treating the surgical field, or polyvidone—iodine solution for 30 s [20] (options).

CSF flow along the drainage system towards the fluid collector should be maintained during the entire duration of CSF drainage, which reduces the risk of infection ascending along the drain [20] (recommendations).

One should avoid retrograde flow of CSF from the fluid collector as the risk of ascending infection increases in this case [20] (options).

Routine replacement of the fluid collector should be avoided because of possible unscrewing of the entire drainage system. The fluid collector should be replaced only after it is more than three quarters full [20] (recommendations).

Wound cleaning that includes hair removal and treatment with aseptic and antiseptic solutions in the site where the external ventricular drainage is placed and the contraincision should be performed at least every 48 h. A dressing consisting of adhesive moisture- and air-tight plaster bandage is recommended [20] (options).

Clinical signs of meningitis (rigidity of occipital muscles, decreased consciousness, developing cranial nerve dysfunction, elevated body temperature (including occasionally)) in patients with an external ventricular drain are the absolute indications for CSF analysis that involves bacterial testing, in addition to the general CSF analysis [27] (recommendations).

The following laboratory data attest to the high probability of intracranial pyoinflammatory complications: cytosis >500/μL, the number of neutrophils with different degrees of decay >80%; low CSF glucose/plasma glucose ratio <0.4; increased CSF protein >0.65 g/L accompanied with high CSF lactate >4.0 mmol/L. The increased level of inflammatory response markers (procalcitonin, >2.0 µg/L) should be additionally taken into account. In complicated diagnostic cases, PCR analysis of CSF to detect DNA of the most plausible
causative agents with allowance for the microbiological situation in the inpatient unit can be performed. Analysis of CSF should be conducted shortly after it was collected because CSF is hypomolar and cell count decreases by 35% during the first hour and up to 50% during the second hour. Analysis of CSF should involve cell counting and morphological classification of cell composition, determining the protein, glucose, and lactate levels. In case of external ventricular drain infection, the drain should be removed [20, 33]. In case of shunt-dependent condition, the drain should be placed again through the non-infected tissues via a subcutaneous tunnel (>5 cm). In patients with pyoinflammatory complications caused by multidrug-resistant Acinetobacter, refusal of drain replacement is associated with increased mortality rate [20, 33] (options).

It is mandatory to obtain the CSF culture results and determine antimicrobial resistance when treating intracranial pyoinflammatory complications. Empiric antibiotic therapy is required if lumbar puncture cannot be performed or CSF cannot be collected from the ventricular drain, as well as before CSF culture results are obtained. The preferred empirical therapy is the therapy with parenteral administration of Ceftriaxone (2 g every 12 h) or Cefotaxime (2 g every 6 h). The alternative empiric therapy regimen includes Meropenem (2 g every 8 h) combined with Vancomycin (60 mg per kilogram bodyweight per day – long-term infusion). This empiric therapy regimen is preferred in inpatient units with the high incidence rate of penicillin-resistant and/or cephalosporin-resistant hospital-acquired infection [26]. In particular instances, antimicrobial drugs can be administered intrathecally in patients with aggravated course of meningitis and in the absence of contraindications. Intrathecal administration of specially adjusted antibiotic salts: vancomycin (10—20 mg/day), gentamycin (4—8 mg/day), tobramycin (5—20 mg/day), amikacin (50—30 mg/day), polymyxin B (5 mg/day), and colistin (10 mg/day) [33]. After intrathecal administration of antibiotics, the external drain should be kept closed for at least 1 h [20]. Patients receiving intrathecal antibacterial therapy should permanently undergo monitoring for neurotoxic events, such as aggravation of meningeal symptoms, suppression of consciousness, partial or generalised seizures [20, 33] (options).

3.11. Nutrition in patients with severe TBI

The TBI patients in critical state should receive early nutritional support satisfying his/her needs for protein and energy. The basal metabolic rate in patients with severe TBI is 20—25 kcal/kg per day. Indirect calorimetry should be used to accurately assess the energy demand of patients. If no metabolograph is available, the energy demand of patients is calculated using formulas. Both enteral and parenteral nutrition can be given. The advantages of enteral feeding over the parenteral one include the lower risk of developing hyperglycaemia and infectious complications. A nasogastric or an orogastric tube is inserted to provide enteral feeding. If the gastric feeding variant for 2 days proves inefficient, a small-bowel feeding tube is inserted. In this case, specialized semi-elemental formulas should be used to feed the patients. A gastrostomy tube can be placed if long-term enteral tube feeding for more than 4 weeks is required [1, 26, 34—36] (recommendations).

3.12. Anticonvulsant therapy

TBI is the main cause for developing epilepsy in middle-aged patients. Posttraumatic seizures include single or repeated seizures that first manifested after the TBI. Seizures can be classified as acute-phase (manifesting within the first 12 h), early (within 7 days), and late (more than 1 week) posttraumatic epilepsy. Other potential reasons for developing epilepsy should be ruled out (especially in the acute phase of the injury): electrolyte imbalance, alcohol intoxication, the past medical history of epilepsy, etc. Epilepsy can be diagnosed based on the clinical presentation of a seizure (according to the evidence by eyewitnesses or a video of a seizure) confirmed by routine EEG recording, video-EEG monitoring for 24—72 h and monitoring plasma prolactin level during the first hours after the seizure.

Status epilepticus is the generalized seizure lasting longer than 5 min or a series of seizures between which the patient remains unconscious. Status epilepticus requires immediate alleviation by administering anticonvulsants. Alleviation of seizures should be started with intravenous injection of drugs. If an agent is unavailable in an intravenous form, it is administered through a gastric tube. A combination of anticonvulsants should be used if monotherapy proves to be inefficient. Myorelaxants are not anticonvulsants; they alleviate only the muscular component of seizures and are used temporarily if a patient needs to be synchronized with the mechanical ventilation system.

Results of class I studies have proved that preventive therapy with phenytoin, carbamazepine, phenobarbital, or valproates is inefficient for preventing late posttraumatic seizures (standard). Anticonvulsants (phenytoin and carbamazepine) are indicated for patients with high risk of developing early seizures during the acute-phase TBI. The risk factors include the presence of foci of cortical contusion, depressed skull fractures, intracranial hematomas, penetrating head injury, and development of a seizure within 24 h after injury (options). Anticonvulsant therapy is prescribed to patients diagnosed with posttraumatic seizures, which can be stopped gradually provided that seizures have not occurred for two years (an option).

3.13. Neuroprotective therapy in the acute phase of severe TBI

As opposed to the experimental studies, there is very little evidence for the effectiveness of neuroprotective drugs in clinical practice. Molecules with different biochemical activity have been considered among the possible neuroprotective agents: inactivators of free radical mechanisms (polyethylene glycol superoxide dismutase — PEG SOD, α-tocopherol, melatonin, etc.), inactivators of carboxyl groups (D-penicillamine, carnosine, aminoguanidine), activators of glutathione synthesis (N-acetylcysteine, gamma-glutamylcysteine ethyl ester), steroids (progesterone, methylprednisolone), calcium channel blockers (Nimodipine), immunosuppressants (cyclosporine A), and modulators of excitotoxicity.

Only few of the aforesaid molecular agents have been tested in clinical trials in patients with severe TBI. PEG-SOD was one of the first agents to be studied; phase II trials demonstrated that it exhibited a positive effect on reduction of the frequency rate of unfavorable outcomes (a persistent vegetative state and death) compared to placebo; however, this
effect has not been confirmed in the phase III trials. In the phase II trials (SYNAPSE), progesterone has shown good effectiveness in reducing the mortality rate and improving the outcomes according to the SCG score 3 and 6 months after injury compared to the placebo group; however, results of the phase III study (PROTECT III) revealed no intergroup difference. The phase II study of cyclosporine A has also yielded promising results; however, the phase III study will be finished only in 2018. A meta-analysis performed by the Cochrane Community for Nimodipine has found that this agent can be used to reduce the risk of fatal outcome only in the group of patients with subarachnoid hemorrhage. Efficacy of the bradykinin antagonists (Deliblant), modulators of excitotoxicity (dexamabnil), magnesium sulfate and its analogue, Selfotel, has been refuted by clinical trials.

Hence, none of the few neuroprotective agents that have made their way to phase III clinical trials has shown efficacy in actual clinical practice. The remaining agents require planning and conducting new multicenter, randomized, placebo-controlled trials. However, the extremely narrow therapeutic range is a significant limitation of their application that is difficult to overcome.

Authors declare no conflict of interest.

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PROBLEMS OF NEUROSURGERY NAMED AFTER N.N. BURDENKO 1, 2016
Awake craniotomy


Burdenko Neurosurgical Institute, Moscow, Russia

Awake craniotomy is a neurosurgical intervention aimed at identifying and preserving the eloquent functional brain areas during resection of tumors located near the cortical and subcortical language centers. This article provides the review of the modern literature dealing with this issue. The anatomical rationale and data of preoperative functional neuroimaging, intraoperative electrophysiological monitoring, and neuropsychological tests, as well as the strategy of active surgical intervention are presented. Awake craniotomy is a rapidly developing technique aimed at both preserving speech and motor functions and improving our knowledge in the field of speech psychophysiology.

Keywords: awake craniotomy, intracerebral tumors, functional area, Broca’s area, Wernicke's area, electrophysiology

“Awake craniotomy” is a quite well-established term in the scientific literature and implied neurosurgical interventions, which are carried out using patient’s awakening from anesthesia in order to control the preservation of certain functions (speech, movement, vision, counting, writing etc.), typically using electrophysiological brain stimulation techniques. The technique of intraoperative electrical stimulation in modern neurosurgery was first published by W. Penfield [1] in 1937, who used it during interventions for epilepsy near the speech cortical areas. In the 1970s, N. Whitaker and G.A. Ojemann [2, 3] improved the technique, using pulse biphasic impulses, and optimized intraoperative tests. In the 1990s, V. Berger [4, 5] applied the awake craniotomy in the surgery of brain tumor near the speech cortical areas. Finally, N. Duffau [6] pointed out the importance of protection of not only the cortical centers, but also axonal pathways connecting the speech centers with motor areas and other areas of the cortex. During the next two decades, the method became widely used in the neurosurgical clinics worldwide. V.A. Loshakov, A.Yu. Lubnin, and G.A. Schekut’ev were the pioneers of awake craniotomy in Russia; they implemented this technique in the surgical practice at Burdenko Neurosurgical Institute at the turn of XXIth century [7, 8].

Indications for the use of surgical techniques with intraoperative awakening and identification of language areas include space-occupying lesions located in the projection or in the immediate vicinity of the cortical speech centers (including tumors and arteriovenous malformations), and epilepsy surgery, such as temporal lobectomy in the dominant hemisphere.

Limitations (contraindications) for this technology include mainly patient’s incapability of performing appropriate tests as a result of severe speech disorders or other reasons, such as fear of intraoperative awakening and pronounced mental disorders, which prohibit required intraoperative interactions. Relative contraindications include anatomical features of diffuse tumor growth directly in the projection of functional areas of the left hemisphere. In this case, the operation is actually limited to the open biopsy of the tumor.

Neuroanatomy of the language cortical areas

In the context of current trends of microneurosurgery, using furrows, brain cisterns, or the projectional local incision of certain gyri to access the pathological lesions, understanding of anatomy and functional significance of certain sulci and gyri is absolutely essential. Since we discuss awake neurosurgery for mass lesions located near the speech centers, we should outline typical anatomical structures of the brain associated with language function.

In most people, motor (Broca’s) and sensory (Wernicke’s) speech centers are located on the lateral surface of the cortex of the dominant hemisphere (mostly the left one) near the Sylvian fissure [9, 10]. In this case, the most important anatomical landmarks include (Fig. 1):

- Sylvian fissure (denoted as SF in the picture);
- Rolando fissure, which in its lower part projectionally “splits” the Sylvian fissure into two roughly equal parts (SulC);
- precentral (SulPrS) and postcentral (SulPoC) gyri located anterior and posterior to the Rolando fissure;
- inferior frontal gyrus (we will discuss its structure in more detail).

The structure of the inferior frontal gyrus is variable, but it is typically split by the terminal bifurcation of the Sylvian fissure to form triangular and opercular portions. Thus, it consists of (in the anterior-posterior direction) orbital, triangular, and opercular parts. In its anterior portion, inferior frontal gyrus merges with the anterior portion of the medial frontal gyrus. In its posterior portion, it is connected to the inferior part of the precentral gyrus. The horizontal and the ascending anterior rami of the Sylvian fissure, originating at the same point, form the triangular part of the inferior frontal gyrus, which is usually more anatomically distinguishable than the opercular and orbital parts. Opercular part is U-shaped. The point where Sylvian fissure bifurcates to the ascending and horizontal rami is called the anterior Sylvian point. Consequently, the anterior Sylvian point is located inferior to the triangular portion and anterior to the base of the opercular part of the inferior frontal sulcus.

In the dominant hemisphere, opercular and triangular parts of the inferior frontal gyrus usually form Broca’s area, the motor speech center. In its posterior portion, U-shaped part of the opercular zone merges with the inferior portion of the precentral gyrus, which corresponds to the major axonal connections with motor areas of the cortex. In some anatomical
types, anterior inferior portion of the opercular zone of the inferior frontal gyrus is quite apparent, because the opercular area is split by an additional small ramus of the Sylvian fissure. This additional ramus runs in the anterior-posterior direction, the so-called diagonal sulcus of Eberstaller, and splits the opercular area into two triangles.

Triangular and opercular parts of the inferior frontal gyrus, which are connected to the precentral and postcentral gyri, cover the superior portion of the insula and form a frontal-parietal operculum. Accordingly, fronto-parietal operculum is located between the horizontal and the posterior ascending parts of the Sylvian fissure [12, 13].

Anteriad, frontal gyri are bounded by the fronto-marginal fissure, separating the suprolateral and orbital surfaces of the frontal lobe.

Temporal lobe is located inferior to the Sylvian fissure. Its posterior portion is bounded by an imaginary line connecting the supra medial part of the parieto-occipital gyrus with the preoccipital gyrus. The lateral surface of the temporal lobe is represented by the superior, medial, and inferior temporal gyri, which are separated by the superior and inferior temporal fissures (running parallel to the Sylvian fissure). Anteriad, medial temporal gyrus terminates before the superior and inferior ones, which merge to form the temporal pole. Since Sylvian fissure usually terminates in the ascending ramus “embedded” into the supramarginal gyrus, the superior temporal gyrus always terminates at the posterior Sylvian point, the end of the Sylvian fissure. Superior temporal gyrus covers the inferior surface of the insula and thus forms the temporal operculum. Temporal operculum and the posterior portion of the superior temporal gyrus in the dominant hemisphere form the representation of Wernicke’s area, sensory speech center. However, there are numerous options for functional cortical representation of the sensory speech center, since this component of speech function involves a lot of other parts of the cortex, such as auditory perception, cortical and subcortical centers of memory, close axonal connection with Broca’s area, and the part of the motor cortex that controls facial and lingual muscles. Therefore, the precise anatomical and functional localization of sensory speech representation is very complicated (Fig. 2). It is believed that speech perception often involves the temporal lobes of both hemispheres (particularly in patients with dominant left hemisphere) [14, 15].

We only touched on the most common issues of the anatomy of the cerebral cortex, corresponding to the present knowledge about the anatomical and functional areas of the speech cortex. Meanwhile, additional anatomical, neuroimaging, and neuropsychological studies are in progress. Intraoperative data collected during operations with awakening are being studied in order to further explore the whole complexity of human speech processes. Let us refer the reader to the recently published review of the pathway anatomy [16].

Preoperative neuroimaging

MRI of the brain in normal mode provides almost real preoperative picture of the individual anatomy of patient’s brain [17]. In the past two decades, functional magnetic resonance imaging (fMRI) of the brain has been developed and used. It is a non-invasive method to identify functional areas zones of the cerebral cortex, i.e. motor, language, and visual ones, and, in recent years, even more sophisticated functions, such as counting, memory, etc. Technically, these methods are based on determining the changes in blood oxygenation level (blood oxygenation level dependent — BOLD) in the areas of the brain, excited by certain functions, such as motor, speech, etc. Of course, the method itself is quite complicated and requires some technical equipment, such as special software, trained staff for accurate data analysis, including their relationship to the neuroanatomy of gyri and sulci with allowance for the possibility their displacement in the presence of a pathological process. This examination results is alignment of fMRI-derived color maps of speech activation and three-dimensional MR anatomy of the brain, which can significantly improve the pre-operative planning (Fig. 3). Despite the rapid development of fMRI, some features of physical and biophysical processes pose significant limitations. Thus, the maximal available anatomical accuracy of determining the anatomical speech areas is currently 10 mm from the center of received signal. Significant distinctive features occur in dextroinsinals, ambidexters, and polyglotism. Therefore, fMRI with identification of Broca’s or Wernicke’s areas cannot be a completely accurate landmark in the intraoperative navigation systems [17].

In recent years, magnetoencephalography (MEG) technique is increasingly widely used. Physically, the method is based on magnetic field measurement. Movement of ions in the cells, intercellular space, and blood vessels results in generation of magnetic fields around neurons, a kind of elementary magnetic generators. The electric current generated due to potential difference between the synaptic terminal and the proximal part of the neuron induces magnetic fields, which are summed up together to produce high enough value for extracranial measurements [18].

Magnetic encephalograph, a device for magnetic encephalography, consists of 3—5 sensors to measure magnetic fields, the computer system, which links these signals to MRI geometry similar to neuronavigation system, and, often, an electroencephalograph for simultaneous recording of EEG. These measurements produce voxel magnetic fields around the entire surface of the scalp. Processing of data about changes in these fields, when a patient follows certain instructions, enables recording and localizing the signals from the motor cortex, speech centers, etc. In recent years, this technology competes in its reliability and data accuracy with functional MRI [19].

Along with fMRI and MEG, MR tractography is a highly valuable method, which facilitates navigation in the anatomy of axonal connections of cortical speech centers with each other and with other functional areas of the cortex, primarily motor tracts.

Clinical and neuropsychological testing

Clinical methods (assessment of neurological deficits, neuropsychological examination, as well as conversation with the patient, explaining the aims and methods of awake intraoperative brain mapping and preparing the patient to cooperate during the surgery [8]) are no less valuable than instrumental techniques in the preoperative examination of patients before operations with awakening.

Neuropsychological examination is the least unified part of this clinical examination complex. However, even in this field, the scientific world tends to normalize preoperative data analysis in order to achieve more accurate assessment of the immediate and long-term post-operative changes in patient’s neuropsychological function [20]. The so-called mini-mental state examination (MMSE) is a pretty simple test. Despite its
Figure 1. Anatomical landmarks of speech areas of the dominant hemisphere.

1 — inferior frontal gyrus (triangular part); 2 — junction of the inferior frontal gyrus (tegmental part) and precentral gyrus; 3 — junction of the precentral and postcentral gyri; 4 — junction of the postcentral and supramarginal gyri; 5 — supramarginal gyrus; SF — Sylvian fissure, SulPrC — sulcus precentralis (precentral sulcus); SulC — sulcus centralis (central sulcus); SulPoC — sulcus postcentralis (postcentral sulcus); AHR — anterior horizontal ramus; AAR — anterior ascending ramus; IFS — inferior frontal sulcus; RP — ramus posterior.
relative primitiveness, it is sensitive to evaluate the progression of malignant gliomas [21].

The following additional options are taken into account in the development and selection of specific test systems and testing [22]:

- demographic characteristics (age, sex, right-handedness/left-handedness, education and occupation, cultural development);
- medical history, including previous treatment;
- data from clinical and instrumental examination methods (neurological examination, CT/MRI, EEG, MEG, etc.);
- results of previous neuropsychological examinations;
- prospective patient’s view on the neuropsychological tests given the awareness (full or partial) of his/her own deficit and understanding (experience) of testing purposes.

- in clinical trials sponsored by NCCTG¹, RTOG², EORTC³, and some other organizations, the “battery” of preoperative, intraoperative, and postoperative neuropsychological tests listed in Table 1 was used.

However, the most common intra-operative tests include counting (numbers), naming the days of the week, months, etc., as well as the test for naming the objects, which neuropsychologist shows to a patient (as pictures), who underwent brain electrical stimulation during surgery [21, 22].

**Intraoperative brain mapping**

**Intraoperative functional neuroimaging**

Integration of multimodal images in frameless navigation is widely used in the last decades and is called “functional neuronavigation”.

However, the only randomized study failed to demonstrate the advantage of the use of navigation in the analysis of postoperative results [23]. This can be explained by limitations of preoperative navigation based on fMRI, as well as intraoperative displacement of anatomical structures of the brain (brain shift), postoperative dislocation of the brain (mass effect), major and vast of operation (especially with large tumors).

In order to reduce the effects of intraoperative dislocation of brain structures, it has been suggested to use certain technical innovations, whose reliability is still being improved: real time three-dimensional intraoperative ultrasound, the use of mathematical models based on the ultrasound data and digital studies capable of cortical shift monitoring, and intraoperative MRI. However, their actual role in the improvement of methods of optimal extent of tumor resection and maintaining patient’s quality of life is still to be studied.

Currently, invasive electrophysiological methods are the “gold standard” for operations in the functional areas of the brain.

**Evoked potentials and electrocorticography**

Evoked potential technique aimed at somatosensory and motor mapping is widely used in the past decade. However, the reliability of this method with respect to localization of Rolandic fissure is not optimal; the accuracy of this method is 91 to 94%. Estimated overall sensitivity and adverse effects amount to approximately 79 and 96%, respectively [24]. Furthermore, phase reversal method facilitates finding the location of Rolandic fissure, but provides no information on the distribution of motor functions in the neighboring areas subjected to the surgery. And although the motor evoked potential technique has been improved, it enables evoked...
potential recording only in monitored muscles, but does not allow detection and prevention of possible deficit in the muscles not subject to monitoring. Monitoring of motor evoked potentials does not include the assessment of complex movements and voluntary movements, which are the ultimate goal of patient's physical activity. Further limitation of this method is that it cannot be used to monitor speech functions, memory, and other higher brain functions, which are of key importance for patient's quality of life.

Recent developments in electrophysiological signal interpretation, such as spectral analysis and electrocorticography, evaluating process synchronization, enabled better understanding of the organization of functional cortical areas and studying their interactions. However, extraoperative electrophysiological monitoring involves grids with electrodes located at a distance of 1 cm from each other, which limits the accuracy of the study. Further inconvenience of this method is the need for two surgical procedures: the first one for grid implantation, and the second one for tumor resection. Since the subdural grid is installed for several days, there is a risk of infectious complications [24, 25].

This method is well suited for the surgical treatment of epilepsy, as it allows detecting the epileptic focus. Electrocorticography provides information about the processes occurring in the cerebral cortex, but it provides no information about axonal connections, so there is no way to assess the subcortical structures and this fact limits the use of this technique in neurosurgery, since gliomas can migrate along the white matter fascicles [25].

**Electro-stimulation mapping of cortical fields and conduction paths**

Given the limitations of the aforementioned techniques, most neurosurgeons currently suggest the additional use of intraoperative electro-stimulation mapping of the functional areas, which may be carried out under general and local anesthesia [26—31]. In patients with tumors affecting the motor area, surgery is performed with cortical field mapping under local anesthesia. However, since movement is more complex process than individual muscle contractions, it is currently recommended to perform intraoperative electro-stimulation mapping with the active participation of the patient in patients with tumors that involve not only the motor area [32].

This method is based on the use of electro-stimulation mapping to obtain the individual map of the cortical and subcortical levels in order to find out, which of the structures involved in the process are really functionally important (in 15—20% of cases of low-grade gliomas the functional significance of these zones in reduced).

The results obtained in this way enable planning the extent of the surgery in accordance with functional boundaries. The technique is as follows. Bipolar electrodes conducting biphasic current are spaced 5 mm apart and applied to the brain substance. Current intensity is adjusted individually for each patient. Baseline value is 2 mA followed by 1 mA increment until the response is obtained. Maximum current strength is 6 mA with local anesthesia and 16 mA with general anesthesia. Higher values may cause seizures. The patient is not informed about the time of stimulation. The same area is not stimulated twice in a row to avoid the development of seizures. Each area of the cerebral cortex, which is available for the study, is stimulated three times [26].

Interestingly, according to a recent study, the surgery can be simplified in the case of the refuse to use intraoperative electrocorticography, since electrical mapping provides equivalent reliably and does not increase the incidence of seizures. Nevertheless, in the case of seizures induced by stimulation, the use cold Ringer's solution is advisable to stop seizure activity [27, 28].

Some authors [29, 30] emphasize the role of “negative mapping” (without identification of eloquent areas). This approach is acceptable in the case of high-grade gliomas (surgery is aimed at removing the bulk of the tumor). However, in the operations for low-grade diffuse gliomas, especially at non-specialized institutions, “negative mapping” can be unsafe. Since low-grade gliomas often have no clear boundary, the extent of resection largely depends on functional criteria. Furthermore, “negative mapping” method may give false negative results and therefore does not guarantee the absence of functional areas. For example, according to N. Sanai et al. [30], all 4 patients who developed permanent postoperative neurological deficits had no functional areas identified prior to resection. For this reason, other authors suggest making approach with more extensive bone flaps in order to perform more precise systematic mapping before the resection [27, 33, 34]. Importantly, “positive mapping” extends resection boundaries and resection may be performed right up to the eloquent area, i.e. without preserving tissue around these zones. A recent study, including 115 patients with low-grade gliomas located in the left dominant hemisphere, showed that the incidence of persistent neurological deficit did not exceed 2%, despite the fact that resection was carried out close to the speech areas [27]. Indeed, S. Gil Robles and N. Duffau [35] have shown that it is not necessary to keep the distance of 5—10 mm to the functional areas, as recommended in the classical literature. These authors state that it is illogical to leave a small tumorous area of the cortex, when the resection is carried out at the subcortical level and involves the pathways of this area, since, although the cortex remains intact, it is excluded and its physiological processes will not restore in the future.

Intraoperative electro-stimulation mapping of motor functions (under general anesthesia, it causes uncontrolled movements, and in awake operations it causes motor disturbance), somatosensory functions (detection of dysesthesia reported by the patient during awake operation), visual function (development of visual field deficiency), audiovestibular function (dizziness), language function (spontaneous speech, counting, naming objects, understanding of speech, writing, reading, switching from one language to another), as well as the mapping of higher mental functions such as mathematical problem solving, memory, spatial orientation, and emotions. Importantly, speech therapist, neurologist, or neuropsychologist should be present in the operating room in order to accurately interpret the detected disorders caused by intraoperative electrical stimulation, such as speech delay, anarthria, oral apraxia, articulation disorders, semantic paraphasia, anomie, and syntax errors [6, 36, 37]. Therefore, intraoperative electro-stimulation mapping provides preoperative real-time detection of the location of functional areas and facilitates the choice of the best surgical approach of tumor resection within these areas.

Another important task is mapping of the subcortical structures along with examination of the cortex prior to resection. Brain damage studies suggest that damage to the pathways is followed by the development of more severe neurological deficits than in the case of cortex injury. Consequently, the pathways supporting motor, somatosensory,
modeling in order to have a coherent idea of which areas of the perioperative functional neuroimaging and biomathematical be used in combination with new techniques, such as However, because of the risk of false-positive results, it should prevent from false-negative results. Indeed, IEM is a highly sensitive method to detect important cortical and axonal structures and provides a unique possibility to study brain connections, since each area responding the stimulus is a part of a large network, rather than a separately operating structure. However, the use of IEM is not an optimal solution. This is due to possible reverse propagation of electrical stimulus or functional compensation due to brain plasticity, which can lead to false positive results.

IEM is considered the “gold standard” of brain mapping. However, because of the risk of false-positive results, it should be used in combination with new techniques, such as perioperative functional neuroimaging and biomathematical modeling in order to have a coherent idea of which areas of the brain are functionally important, and which can be compensated.

### The strategy and tactics of awake operations with intraoperative brain mapping

#### Preoperative planning and intraoperative neurosurgical strategy

Along with the aforementioned detailed and careful preoperative examination, surgery of mass lesions near or in the projection of speech centers of the brain and pathways of these eloquent functional areas of the brain requires thorough planning of neurosurgical operations, including accurate specification of the extent of the transcranial approach and determining cortical anatomical landmarks (major sulci and gyri, large convexital veins etc). Thus, N. Duffau, one of the leaders of this trend in neurosurgery [41], suggests the following important objectives of intraoperative electrical stimulation of the cerebral cortex:

- to study individual functional cortical organization prior to resection;
- to understand the pathophysiology of brain areas, located in the projection of the tumor;
- to compare the subcortical structures in the projection of resection and to study anatomical and functional relationships;
- to analyze the mechanisms of on-line (intraoperative) brain plasticity, using repeated electrical stimulation at all stages of tumor resection;
- to perform resection with allowance for individual disturbance of cortico-subcortical functional boundaries. The
main objective of this is to optimize the ratio of radicality of the surgery and the risk of exacerbation of neurological deficit.

When using neuronavigation systems, neuronavigation data are used both for planning of trepanation and for the preliminary assessment of the relative location of cortical speech centers after dura mater opening. Furthermore, it is important to compare the results of intraoperative electrical stimulation to the perioperative functional neuroimaging (before and after the surgery) in order to confirm these non-invasive methods and for better understanding of short-term and long-term mechanisms of brain plasticity based on functional cortical reorganization and change in “network” connection [42]. It should be remembered that, because of the virtual neuronavigation technique, the accuracy of neuronavigation data is significantly reduced with mass lesion resection due to displacement of the brain substance.

Dura mater opening during awake operations is carried out in such a way that to open the entire surface of the brain in the projection of trepanation opening with a view of the widest possible intraoperative electrophysiological mapping [43].

**Intraoperative electrostimulation technique**

After dura mater opening, multipolar electrode for direct corticography is placed (for the purpose of intraoperative control of seizure activity of the cerebral cortex) in such a way that it did not interfere with surgical procedures (it is usually placed subdurally outside the trepanation opening).

Electrophysiological mapping should be carried out with the participation of anesthesiologist, electrophysiologist, neuropsychologist, and operating neurosurgeon.

By the time of electrostimulation of the brain aimed at direct identification of cortical speech centers, the patient must be awake out of anesthetic sleep. Further, stable verbal and psycho-emotional contact should be established with the patient.

Cortical area remote from tentative Broca’s and/or Wernicke’s area should be selected to adjust electrostimulation current. After current adjustment, the mapping itself should be carried out.

The entire opened surface of the cerebral cortex should be consistently studied starting from the supposedly “silent” regions to the functional areas. When detecting errors in test execution during intraoperative neuropsychological testing (see relevant sections), the procedure should be paused and then stimulation should be repeated 1—2 times in the area identified as a cortical speech center. Cortical speech areas identified using direct electrical stimulation should be marked with sterile paper (cellulose) labels with numbers (Fig. 4) [7, 8].

Seizure activity of the cerebral cortex should be monitored during the entire electrical stimulation procedure. In the case of readiness for convulsions, electrical stimulation of the brain is stopped, and surgical wound is irrigated with prefabricated cooled saline solution, and intravenous anticonvulsants are administered, if necessary (not barbiturates, except for the development of life threatening seizures): sodium valproate and/or levetiracetam [8].

Electrical stimulation of motor areas of the cortex is carried out either during the search for cortical speech areas, or, additionally, motor cortical centers in the case of anatomical spread of space-occupying lesions in the direction of the motor cerebral convolutions. The areas of the motor cortex are also labeled with numbered cellulose piece (see Fig. 4).

**Postoperative examination**

Within 24 hours after the surgery, CT and contrast-enhanced (if the space-occupying lesion accumulated contrast agent) or non-contrast-enhanced (if the tumor was not contrasted according to the preoperative data) MRI of the brain should be carried out in order to exclude intraoperative bleeding complications and complications in the early postoperative period. This postoperative study is aimed at assessing the degree of radicality of tumor resection (including volumetric comparison, if possible). Within the first few days after the operation, repeated neuropsychological study should be done and then it should be repeated during a follow-up examination in 3 and 6 months, and in the long-term follow-up, if possible.

The outcomes of operations with intraoperative awakening When comparing general results of operations with and without intraoperative awakening in cases with similar
anatomical location of the tumor, it should be admitted that the literature provides no clear evidence neither in favor of the use of this technique, nor against it. The case is that in some major neurosurgical centers almost all operations for the tumors located near the speech areas are performed with the awakening, while in the other ones, on the contrary, awake craniotomy is not widely used. And finally, the third group of clinics alternately use both approaches, without giving significant preference to any of them.

To finalize our detailed overview of methodological approaches to the use of the technique of operations with intraoperative awakening and speech area mapping, let us consider the data of meta-analysis performed by a group of researchers, who focused on a wider problem, i.e. the use of intraoperative electrophysiological mapping of both speech areas with awakening and motor areas without awakening compared to operations without the use of intraoperative electrophysiology. The results of this study are shown in Table 2.

This meta-analysis shows that the use of intraoperative mapping of eloquent areas of the brain (motor cortex, speech areas, etc.) can provide significantly better results in terms of decreased incidence of persistent neurological deficit (about 2.5-fold) compared to the operations without intraoperative mapping. In this case, better outcome is achieved by no means at the expense of lower radicality of tumor resection. The authors of these works concluded that intraoperative electrophysiological mapping has become the gold standard for operations near the eloquent areas of the brain [45].

Conclusion
Prospects of the development of surgical methods with intraoperative awakening
Currently, the accumulated experience of awake operations, development of functional neuroimaging techniques, and rapid development of intraoperative electrophysiological mapping enables the use of awake operations not only for the purpose of cautious handling of cerebral centers and pathways of speech and motor structures, but also to preserve the visual centers and pathways of the visual analyzer.

In this review, we deliberately did not touch the issues of anesthetic management of awake craniotomy, since this part of the problem is covered in the works of our colleagues [7, 8]. However, let us note that our neuroanaesthesiologists have priority in publication of materials on the use of xenon anesthesia for awake operations in the scientific world. [46]

It should be emphasized that awake neurosurgical operations near speech areas and other functional centers of the brain using the active multidisciplinary approach contribute to the development of our knowledge in the field of functional structure of the brain centers of speech, memory, counting, writing, hearing, and visual perception and other higher neural functions.

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