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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,
Burdenko’s Journal of Neurosurgery 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.
Clinical and MRI predictors of coma duration, intensive care and outcome of traumatic brain injury


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Abstract

Objective. This research is aimed to study the clinical and MRI predictors of coma duration, the intensity of critical care, and outcome of traumatic brain injury (TBI).

Materials and methods: The data from 309 patients with TBI of varying severity were included in the analysis, of whom 257 (86.7%) were treated in the intensive care unit (ICU), including 196 (63.4%) patients admitted in a comatose state lasting longer than 1 day. All patients underwent brain MRI within 21 days after the injury. MRI findings were classified according to MRI grading scale of brain damage level/localization proposed previously.

Results. The proposed MRI grading significantly correlated with the Glasgow coma (GCS, r=-0.67; p<0.0001) Glasgow outcome (r=0.69; p<0.001) scores in the entire group. In a subgroup of comatose patients (GCS<9) it correlated with coma duration (r=0.52; p<0.0001). Spearman correlation analysis showed a significant relationship between the MRI classification and a number of parameters: ICU length of stay (r=0.62; p<0.0001), the duration of artificial ventilation (r=0.47; p<0.0001), the rate of artificial ventilation, sedatives, analgesics, mannitol, a hypertonic solution of sodium chloride and vasopressors usage (p<0.01). These data confirm the relationship between higher grades of MRI classification (deep brain damage) and the need for the escalation of intensive care main components.

Conclusion. Our results support the hypothesis that the levels and localization of brain damage, estimated by the proposed MRI grading scale, might be predictors of coma duration, intensity, and duration of intensive care and TBI outcomes. A prognosis based on clinical and neuroimaging data comparison can be valuable for planning and efficient use of the hospital beds and ICU resources, for optimizing the patient flow and timing of patient transfer to neurorehabilitation facilities.

Keywords: traumatic brain injury, magnetic resonance imaging, classification, intensive care, outcome.

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Abbreviations

ICH — intracranial hypertension
MRI — magnetic resonance imaging
ICU — intensive care unit
TBI — traumatic brain injury
GOS — Glasgow outcome scale
GCS — Glasgow coma scale
Various authors reported high prognostic value of magnetic resonance imaging (MRI) for traumatic brain injury (TBI) [1—10]. The authors of this manuscript have previously analyzed the relationship between severity/outcomes of TBI and the level and localization of injuries verified by MRI [5, 7, 8]. Analysis of MRI data in 162 patients within 3 weeks after TBI ensured development of a classification of TBI severity depending on the level and localization of damage to hemispheres, cerebellum and brain stem structures (MR classification).

According to this classification, the following categories were distinguished: 1 — no damage, 2 — cortico-subcortical lesion of hemispheres or cerebellum; 3 — corpus callosum injury not excluding damage category 2; 4 — damage to basal ganglia or thalamus not excluding category 2—3; 5 — unilateral brainstem damage at any level not excluding category 2—4; 6 — bilateral midbrain damage not excluding category 2—4; 7 — bilateral pontine damage not excluding category 2—6; 8 — bilateral damage to medulla oblongata not excluding category 2—7. T1, T2, T2-FLAIR, DWI, T2 * GRE, SWAN sequences were used to detail all types of non-hemorrhagic and microhemorrhagic lesions. MR data on TBI severity significantly correlated with clinical severity according to GCS and GOS scores. Thus, MR classification was included into the clinical recommendations for the diagnosis and treatment of severe TBI [11—13]. Further examination of 278 patients in accordance with the proposed MR protocol revealed significant correlation between MR grades, GCS and GOS scores within 3 days and 3 weeks after injury [14]. Moreover, accuracy, sensitivity and specificity of MR classification in predicting the outcome of TBI were confirmed by logistic regression and ROC analysis. It should be emphasized that correlation of MR grades with GOS/GCS scores is especially valuable if assessment of GCS score is difficult or impossible (for example, severe periorbital edema or hematoma, intubation or tracheostomy with mechanical ventilation, need for sedation and analgesia or their combination). Another variant is TBI under drug (or alcohol) intoxication.

Considering these data, we supposed that localization and level of brain damage, estimated in accordance with the proposed MR classification, can predict duration of coma, ICU-stay, outcomes, length of hospital-stay and subsequent rehabilitation in patients with severe TBI.

The aim of the study was to analyze clinical and MR predictors of coma duration, intensive care and ICU-stay, outcomes in patients with TBI.

In our opinion, this prognosis based on neuroimaging data could be useful for effective use of bunks at the intensive care unit, material resources, optimizing the flow of patients and their subsequent transferring to rehabilitation centers.

**Material and methods**

An analysis included 309 patients with TBI who admitted to the Burdenko Neurosurgery Center for the period from 2001 to 2019. MRI was performed upon admission in all cases in addition to routine computed tomography (CT). Indications for MRI were formulated through the consensus of specialists. These indications included

![Fig. 1. The distribution of patients with TBI by Glasgow Coma Score (a) evaluated on admission to N.N. Burdenko Neurosurgery Center and duration of coma (b).](image-url)

Red dotted line indicates mean value.
inconsistency of CT data and neurological status or its dynamics, clarifying the localization and type of brain damage. Mandatory requirements for MRI were absence of metal implants, informed consent of relatives or the patient himself (in a clear mind), regression of psychomotor agitation and restoration of adequate behavior in patients with mild-to-moderate trauma. Additional requirements for MRI in patients with severe TBI included hemodynamic stabilization, normalization of intracranial pressure (ICP), available monitoring and vital support during transportation and examination. Inclusion criterion was also available assessment of GCS score at admission and GOS score in 6 months after injury via direct contact with the patient or interviewing of the relatives. Thus, 309 patients were selected (16.4% of all patients admitted with acute TBI for this period). Mean age of patients was 29 (21; 39) years. There were 220 (71.2%) men and 89 (28.8%) women. MRI was performed within 1–21 days (mean 10.0±5.9 days) after TBI using 1.5 T (Signa Exite General Electric, USA) and 3.0 T MRI scanners (Signa HDxt General Electric”, USA) in accordance with the protocol described in the previous manuscripts [5–7, 14].

Victims were transferred to the Burdenko Neurosurgery Center from the emergency hospitals in Moscow, Moscow Region, and other regions of the Russian Federation within 2.5±2.2 days after injury. TBI was caused by road accident in 197 (63.8%) patients, drop — in 53 (17.2%) cases, blows to the head and others — in 59 (19%) victims. Isolated TBI was observed in 181 (58.6%) victims, combined trauma — in 128 (41.4%) cases. Blunt injury was diagnosed in 204 (66%) patients, open trauma — in 105 (34%) cases including penetrating TBI in 74 (24%) cases. In 58 (18.8%) patients, evacuation of intracranial hematoma and/or elimination of cranial vault fractures followed by brain compression were carried out at the emergency hospitals.

GCS score without sedation ranged from 3 to 15 points (median 7; 6; 12) points at admission to the Burdenko Neurosurgery Center. Duration of coma was determined until the first signs of restoration of consciousness (spontaneous eye opening or in response to voice/pain, following simple instructions, answering a question).

In accordance with the clinical guidelines [11–13, 15–18], invasive ICP sensors were inserted in 159 (51.5%) patients. Considering clinical, CT data, monitoring of intracranial and cerebral perfusion pressure, 71 (23.0%) patients underwent various surgical interventions aimed at brain decompression (osteoplastic craniotomy, unilateral and bilateral decompressive craniotomy, external ventricular drainage).

Focal or diffuse hemorrhagic or non-hemorrhagic brain injury, subarachnoid, intracerebral, intraventricular hemorrhages, epidural and subdural hematomas and hygroma, brain cistern compression and lateral displacement of the median structures were verified by using of CT/MRI data.

MRI data were analyzed in accordance with the previously proposed classification (gradation) of localization and level of brain damage [5, 8, 14].

Statistical analysis was carried out using statistical programming language and R environment (version 3.6.1) in the IDE RStudio (version 1.2.1335). Continuous and discrete quantitative variables were described using mean values, standard deviation, median and quartiles, categorical values — as percentage. Statistical hypotheses about the differences of quantitative variables in independent samples were tested using the nonparametric Mann — Whitney test. Differences of categorical variables were analyzed using Chi-square test and Fisher’s exact test. Correlation between the quantitative values was evaluated using Spearman correlation coefficient. Predictors of the outcomes were assessed using multivariate analysis with linear regression and binary logistic regression (300-fold resampling and training sample size of 80% of the original one). The confidence intervals for area under ROC curve (ROC_AUC) were estimated using Bootstrap technology (1000 iterations). The null hypothesis was rejected at p-value <0.05.

**Results**

GCS scores upon admission are shown in Fig. 1a. Coma (3–8 points) was observed in 196 patients, stupor and severe obtundation (9–12 points) — 40 (13.0%) patients, moderate obtundation or clear consciousness (13—15 points) — 73 (23.6%) patients. Mean duration of coma was 10.6±6.6 days (Fig. 1b), ICU-stay — 26.7±25.4 days, hospital-stay — 55.4±65.3 days.

MRI grading of patients is shown in **Table 1**.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of patients, n (n=309)</th>
<th>Proportion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No damage</td>
<td>29</td>
<td>9.4</td>
</tr>
<tr>
<td>2 Cortical-subcortical lesions of hemispheres or cerebellum</td>
<td>76</td>
<td>24.6</td>
</tr>
<tr>
<td>3 Corpus callosum lesions (lesions assigned to Grade 2 not excluded)</td>
<td>32</td>
<td>10.4</td>
</tr>
<tr>
<td>4 Basal ganglia, thalami lesions (lesions assigned to Grades 2—3 not excluded)</td>
<td>28</td>
<td>9.1</td>
</tr>
<tr>
<td>5 Any unilateral brain stem lesions (lesions assigned to Grades 2—4 not excluded)</td>
<td>55</td>
<td>17.8</td>
</tr>
<tr>
<td>6 Bilateral midbrain lesions (lesions assigned to Grades 2—4 not excluded)</td>
<td>56</td>
<td>18.1</td>
</tr>
<tr>
<td>7 Bilateral pons lesions (lesions assigned to Grades 2—6 not excluded)</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>8 Bilateral medulla oblongata lesions (lesions assigned to Grades 2—7 not excluded)</td>
<td>2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Table 1. The distribution of patients by MRI grades of brain damage level and localization (n=309)**
There were fewer patients in categories 1, 3, 4, 7 and 8 categories compared to 2, 5, and 6. Corpus callosum injuries were observed in 190 (61.7%) patients, cortical-subcortical damage — 181 (58.8%), subcortical nuclei — 112 (36.4%), thalamus — 85 (27.6%) patients. Unilateral or bilateral brainstem lesion combined with damage to the overlying brain structures (grades 5—8) was detected in 144 (46.6%) patients. Consequently, the vast majority of patients had MR signs of diffuse axonal damage involving hemispheric and brain stem structures in various combinations. At the same time, there were CT and MRI data on certain intracranial hemorrhages (subarachnoid hemorrhage — 224 (78.6%), intraventricular hemorrhage — 100 (32.4%)) and hematomas (epidural hematoma — 36 (11.7%), subdural hematoma — 114 (36.9%), intracerebral hematoma — 43 (13.9%)) in most patients.

Spearman correlation analysis revealed significant relationship between GCS score and duration of coma in patients with severe TBI ($r=-0.48$, $p<0.0001$; Fig. 2a), GCS score and MRI grade of TBI in the entire group regardless of TBI severity ($r=-0.67$, $p<0.0001$; Fig. 2b), duration of coma and MRI grade of TBI in unconscious patients ($r=0.52$, $p<0.0001$, Fig. 2c).

Severe consciousness impairment (coma) was observed in 196 (76.3%) out of 257 patients who were treated at the ICU. Duration of coma was over 24 hours. Mean ICU-stay was 26.7±25.4 days, hospital-stay — 63.2±68.3 days. There was a significant relationship between MRI grade of brain damage and ICU-stay ($r=-0.62$, $p<0.0001$), hospital-stay ($r=0.61$, $p<0.001$) (Fig. 3).

In accordance with the clinical guidelines, invasive monitoring of intracranial and arterial pressure, assessment of cerebral perfusion pressure, cerebral blood flow and its autoregulation were carried out in 159 (51.5%) patients [19—21]. A retrospective analysis revealed significant relationship ($p<0.001$) between the incidence of ICP monitoring and MRI grade of brain damage (Table 2). There was significant correlation ($p<0.001$) between MRI grade of brain damage and incidence of subarachnoid and intraventricular hemorrhages, as well as signs of secondary brain ischemia (Table 2).

Relationship of localization and level of brain damage with application of various components of intensive care and TBI outcomes

In this part, we have analyzed the relationship between TBI severity, localization and level of injury according to MRI data and intensive care in 257 patients. The main components of therapy including sedation (n=175; 70.3%), analgesia (n=59; 23.9%), muscle relaxants (n=42; 16.9%), hyperosmolar drugs — mannitol (n=76; 30.8%) and hypertonic saline solution (n=46; 18.5%), vasopressors (n=121; 48.8%), barbiturates (n=10; 4.0%), as well as mechanical ventilation (n=228; 88.7%) with hyperventilation mode (n=66; 26.7%), moderate hypothermia (n=17; 6.9%) were considered. Higher need for
the main components of intensive care significantly correlated with more severe TBI according to MR grading system (Table 3).

Spearman correlation analysis revealed significant relationship between duration of mechanical ventilation and MR grade of TBI ($r=0.47, p<0.0001$) (Fig. 4). Similar significant relationship was found between MR grade of TBI and need for hyperventilation ($p<0.001$), administration of sedatives ($p<0.001$), analgesic drugs ($p=0.009$), mannitol ($p<0.001$), hypertonic saline solution ($p=0.005$) and vasopressors ($p<0.001$) (Table 3, Fig. 5). Perhaps, these data confirm the hypothesis that higher MR grade of TBI is associated with more severe brain damage and, accordingly, the need for escalation of intensive care.

**Prognostic value of brain damage MR grading system**

Prognostic significance of the proposed MR grading system regarding hospital-stay and TBI outcomes was analyzed using linear and binary logistic regression. In addition to MR grade of brain damage, the predictors included age, gender, GCS score, need for mechanical ventilation, certain components of intensive care and craniotomy. The quality of prognostic models was evaluated using mean absolute forecast error for timing and ROC analysis for binary outcomes. We calculated sensitivity, specificity, accuracy, completeness and $F$-measure for the model.

Linear regression model of the relationship between hospital-stay of TBI patients and brain damage MR grade, GCS score and some other predictors is shown in Table 4. The coefficient for each predictor shows changes of the length of hospital-stay (days) if the coefficient increases by 1 and all other things are equal (unchanged other predictors). In other words, increased MR grade by 1 category, ceteris paribus, is associated with prolonged hospital-stay by 8.8 days. GCS score augmentation by 1 point is followed by reduced hospital-stay by 4.1 days. Thus, absolute value of the coefficient determines the influence of certain predictor on hospital-stay, and the sign of coefficient determines the direction of this influence.

![Fig. 3. The relationship between MRI classification grades and ICU length of stay ($n=257$) (a), as well as the total length of stay in the neurosurgical hospital for all patients we studied (b).](image-url)

Table 2. The number (proportion) of patients with secondary ischemia, subarachnoid (SAH) and intraventricular (IVH) hemorrhages and those requiring intracranial pressure (ICP) monitoring in each category according to MRI classification ($n=309$).

<table>
<thead>
<tr>
<th>MR grade of TBI</th>
<th>Secondary ischemia* ($n=308), n (%)$</th>
<th>SAH* ($n=285), n (%)$</th>
<th>IVH ($n=309), n (%)$</th>
<th>ICP monitoring ($n=309), n (%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>4 (13.8)</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2.6)</td>
<td>53 (73.6)</td>
<td>8 (10.5)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>3</td>
<td>1 (3.1)</td>
<td>26 (96.3)</td>
<td>9 (28.1)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>4</td>
<td>8 (29.6)</td>
<td>25 (96.2)</td>
<td>11 (39.3)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>5</td>
<td>6 (10.9)</td>
<td>42 (82.4)</td>
<td>23 (41.8)</td>
<td>34 (61.8)</td>
</tr>
<tr>
<td>6</td>
<td>6 (10.7)</td>
<td>45 (91.8)</td>
<td>26 (46.4)</td>
<td>41 (73.2)</td>
</tr>
<tr>
<td>7</td>
<td>11 (35.5)</td>
<td>28 (96.6)</td>
<td>23 (74.2)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>8</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

Note. * the robust data on the subarachnoid hemorrhage and secondary ischemia presence were not available for all patients in a retrospective study.
P-value $<0.05$ indicates significant correlation of hospital-stay with certain predictor.

According to Table 4 data, prognostic significance of MR grading system for the length of hospital-stay is somewhat greater compared to GCS score.

Binary modeling of TBI outcomes (favorable — GCS score 4—5, unfavorable — GCS score 1—3) using logistic regression is shown in Table 5. Thus, brain damage MR grade, GCS score and age are significant ($p<0.0001$) predictors of TBI outcomes with comparable impact on the outcome (absolute value of coefficients). Despite the strong correlation of MR grading system and GCS score ($r=-0.67$, $p<0.0001$), exclusion of any of these predictors worsens prognostic properties of the models.

Pooled results of 300 computational experiments for assessing the model prognosis quality for a favorable (score 4—5) TBI outcome are shown in Table 6. Analysis was based on GCS score (logistic regression) with brain damage MR grade, GCS score and 2 predictors — muscle relaxation ($n=42; 13.6\%$) and mechanical ventilation ($n=228; 73.8\%$) together with other factors significantly associated with TBI outcome. As you can see, the models independently considering GCS score or MR grade of TBI, ceteris paribus, have similar prognostic properties. These data also confirm comparable prognostic value of these models for TBI outcome.

**Discussion**

TBI management is a difficult medical and economic problem requiring expensive diagnostic methods, intensive care and surgery. For example, D. Wright et al. [22] reported direct and indirect costs for the treatment of this lesion near $\$76.5$ billion in the USA in 2010. Significant resources are required for long-term intensive care including multimodal monitoring, dynamic neuroimaging (CT, MRI). Searching for the most reliable predictors of TBI severity and duration of critical period of traumatic brain disease is very important for planning all stages of treatment, surgical interventions, methods and duration of intensive care and subsequent rehabilitation. It is known that GCS score is a significant prognostic factor of brain injury. However, significance of this parameter is impaired in case of severe periorbital edema or hematoma, trauma under drug or alcohol intoxication, in-

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**Table 3. The number (proportion) of patients exposed to different intensive care treatment in ICU ($n=257^*$).**

<table>
<thead>
<tr>
<th>MR grade of TBI</th>
<th>Hyperventilation ($n=247$, $n$ (%)</th>
<th>Analgesia ($n=247$, $n$ (%))</th>
<th>Sedation ($n=249$, $n$ (%))</th>
<th>Mannitol ($n=247$, $n$ (%))</th>
<th>Hypertonic saline solution ($n=248$, $n$ (%))</th>
<th>Vasopressors ($n=248$, $n$ (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>2</td>
<td>7 (13.7)</td>
<td>7 (13.7)</td>
<td>23 (44.2)</td>
<td>8 (15.7)</td>
<td>5 (9.6)</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>3</td>
<td>4 (14.3)</td>
<td>4 (14.3)</td>
<td>18 (64.3)</td>
<td>6 (21.4)</td>
<td>2 (7.1)</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>4</td>
<td>9 (39.1)</td>
<td>9 (39.1)</td>
<td>15 (65.2)</td>
<td>8 (34.8)</td>
<td>7 (30.4)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>5</td>
<td>10 (19.2)</td>
<td>9 (17.3)</td>
<td>44 (84.6)</td>
<td>13 (25)</td>
<td>7 (13.5)</td>
<td>25 (48.1)</td>
</tr>
<tr>
<td>6</td>
<td>19 (36.5)</td>
<td>19 (36.5)</td>
<td>44 (83)</td>
<td>21 (40.4)</td>
<td>13 (25)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>7</td>
<td>16 (55.2)</td>
<td>10 (34.5)</td>
<td>29 (100)</td>
<td>19 (65.5)</td>
<td>11 (37.9)</td>
<td>27 (93.1)</td>
</tr>
<tr>
<td>8</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

*Note.* $^*$ reliable data on treatment components were not available for all ICU patients in a retrospective study.
tubation with mechanical ventilation, need for sedation and analgesia. CT significantly complements TBI diagnosis, but sensitivity of this method is significantly lower for diffuse and, especially, non-hemorrhagic brain injuries compared to MRI. High prognostic value of MRI for analysis of localization and level of brain damage was shown in previous reports [1—6, 8—10, 23—28].

Our sample included 309 patients with TBI, 257 (86.7%) of them required intensive care, coma for more than a day was observed in 196 (63.4%) patients. It was found that MR grading system of brain damage correlates with GCS score, TBI outcome, duration of coma, ICU-stay and hospital-stay. Mean length of ICU-stay and hospital-stay was 26.7 and 55.4 days, respectively.

According to our data, MR classification of brain damage as an indicator of TBI severity may be used as a predictor of intensive care escalation and prolonged ICU-stay. Moreover, it has been recently shown that prolonged ICU-stay in patients after craniocerebral surgery (craniotomy, ICP sensor insertion, external ventricular drainage) and extracranial interventions (tracheostomy, major vessel catheterization, etc.) as well as prolonged mechanical ventilation is a risk factor of various life-threatening infectious complications [29].

It should be emphasized that this research has been carried out over the last two decades. The new data were obtained and clinical guidelines for the diagnosis and treatment of TBI were partially updated throughout this period [11—13, 15—18, 30—33]. At the same time, such basic elements of monitoring and intensive care as ICP invasive control, blood pressure and cerebral perfusion pressure, use of vasopressors, osmotic, sedative and analgesic drugs, indications for mechanical ventilation and moderate hyperventilation remained the same [11—13, 18—20].

A somewhat different situation is observed for decompression operations. Some indications for these interventions are still debatable [16, 18, 32—34].

**Conclusion**

MR grading system of brain damage may be a predictor of coma duration, intensive care escalation, outcomes and length of hospital-stay and subsequent rehabilitation in patients with severe TBI.

In our opinion, a prognosis based on clinical and neuroimaging data may be valuable for planning and efficient use of the hospital beds and ICU resources, optimizing the patient flow and timing of patient transfer to neurorehabilitation facilities.
Authors’ participation: Concept and design of the study — A.P., G.D., N.Z., A.S.

Statistical analysis — G.D., Yu.S.
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Editing — N.Z., A.P., G.D., L.L.

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Resting-state fMRI in preoperative non-invasive mapping in patients with left hemisphere glioma

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Abstract

Maximum resection and preservation of neurological function are main principles in surgery of brain tumors, especially glial neoplasms with diffuse growth. Therefore, exact localizing of eloquent brain areas is an important component in surgical planning ensuring optimal resection with minimal postoperative neurological deficit. Functional MRI is used to localize eloquent brain areas adjacent to the tumor. This paper is an initial stage in analysis of resting-state fMRI in assessment of functional changes of neuronal activity caused by brain gliomas of different localization. We report two patients with glial tumors localized within the precentral gyrus of the left hemisphere and near speech area. Considering data of task-based and resting-state fMRI, as well as direct cortical stimulation, we propose a methodology for assessing the overlap of activations obtained by these methods.

Keywords: brain MRI, functional MRI, resting-state fMRI, preoperative planning, brain mapping.

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Abbreviations

MRI — magnetic resonance imaging
fMRI — functional magnetic resonance imaging
fMRIs — stimulus-dependent functional magnetic resonance imaging
rsfMRI — resting state functional magnetic resonance imaging
Total resection and preservation of neurological function are key principles in surgery of brain tumors, especially glial tumors with diffuse growth. Accurate localization of functionally important areas is an important component in surgical planning because this approach ensures optimal resection with minimal postoperative neurological deficit.

Stimulus-dependent functional magnetic resonance imaging (fMRIs) has been used for more than two decades. This method was applied to determine functional brain areas adjacent to the tumor and based on registration of a BOLD signal (blood oxygen level-dependent) from the active cortical areas during various tests (stimuli, paradigms). Activation of a particular brain region results local hemodynamic changes and oscillations of MR signal.

Neurosurgeons use MR mapping for preoperative planning and analysis of further resection quality. Nevertheless, fMRIs is characterized by several limitations. First of all, it is dependence on patient’s ability to execute adequately and timely the commands laid down into the paradigm [1]. Another limitation of fMRIs is the need to use different stimuli (paradigms) for evaluation of various functions (for example, movement and speech) in accordance with a proportionally increased time of examination.

Resting state functional MRI (rsfMRI) has similar basic principles and is considered as a possible alternative to fMRIs.

Similar to fMRIs, resting state brain activity is considered by changing cerebral blood flow (BOLD signal). Any brain area demonstrates spontaneous oscillations of BOLD signal at low frequencies (less than 0.1 Hz) even in the absence of external stimuli.

It is known that resting state brain is involved into continuous spontaneous activity. This activity is not associated with any stimuli or generation of responses. Research of resting state brain using electroencephalography and fMRI revealed several neural networks which are constantly visualized without external stimulation within one scanning. These networks represent synchronous neuronal activity of certain brain areas. Those brain areas with time-correlating signal changes are considered functionally related. There are several basic neuronal networks: passive mode network, sensorimotor network combining sensory and motor zones, auditory and speech networks. Networks for control of performance, attention, memorization, and so on are also distinguished. Analysis of neuronal networks is a new approach in assessing of functionally related zones, even if they are anatomically distant from each other [2].

The results of rsfMRI showed a high relationship between anatomical brain structures and functional neuronal networks. Recent studies have demonstrated that rsfMRI may be used for neurosurgical planning in patients with brain tumors [3—5]. According to this review, the results obtained by various authors are still preliminary and require additional research (specialized software developments including the choice of analytic methods and resource-intensive processing of MR data).

In this report, we present two patients with glial tumors in the left hemisphere within precentral gyrus (patient 1) and speech zones (Broca, Wernicke, facial muscles) (patient 2). We compared the results of two fMRI methods and direct cortical stimulation. As a result, we proposed a method for determining an accuracy of coincidence of activations obtained by three methods.

Case report 1

A 36-year-old patient B. was hospitalized to the local hospital after a road accident due to focal seizure. CT and MRI of the brain revealed a tumor in the left frontoparietal region with peritumoral edema.

The patient complained of a headache and nausea at admission to the Burdenko Neurosurgery Center a month after accident (November 14, 2018). Physical examination upon admission revealed clear mind, complete and correct orientation, no focal neurological symptoms. There were only general cerebral symptoms. Contrast-enhanced MRI, fMRIs ensuring functional data on motor activation of both hands in accordance with the original protocol and rsfMRI with assessment of sensorimotor network were carried out before hospitalization.

Resection of a tumor of the left frontoparietal region with intraoperative electrophysiological monitoring was performed a month later. Osteoplastic craniotomy in the left frontoparietal region was carried out under endotracheal anesthesia in patient’s supine position. Dura mater dissection was followed by electrophysiological cortical mapping (bipolar electrode with a current strength of 16–20 mA). Motor zone of the right arm was identified dorsally from the tumor. Preoperative fMRIs showed similar data. Mapping data were incorporated into neuronavigation system. In this case, motor zone of the hand was marked in navigation system by several points (4 points on the periphery with activation and 4 points at the distance without activation).

Total resection was performed. According to biopsy data, it was glioblastoma without an identified mutation IDH1 R132H, WHO Grade IV. No postoperative neurological deterioration was observed.

Case report 2

A 48-year-old patient O. was hospitalized to the Burdenko Neurosurgery Center with complaints of mnestic disorders. The disease manifested about 1.5 months ago with headache, memory impairment and transient diplopia. MRI revealed intracerebral tumor of the left frontoinsular region. There were moderate mnestic disorders without any other neurological deficit.

Some additional diagnostic procedures were recognized advisable to determine optimal treatment strategy:
standard MRI before and after contrast enhancement, fMRIs with analysis of speech zones, rsfMRI with speech network assessment, MR tractography with visualization of arcuate and corticospinal tracts in the left hemisphere. Preoperative survey was followed by surgical intervention under electrophysiological monitoring. Neuropsychological examination was also carried out prior to surgery.

Resection of a tumor of the left frontoinsular region was performed under electrophysiological monitoring. Osteoplastic craniotomy in the left frontotemporal region was made under regional anesthesia in patient’s supine position. Dura mater was dissected in X-shaped fashion, and the patient was awakened. Cortical segment with abnormal pattern and vessels was found. Electrophysiological cortical mapping was performed using a bipolar electrode (current strength 4 mA). Stimulation of a zone localized 1.5 cm apically and dorsally from the tumor resulted speech disturbances (motor aphasia). These were lower parts of precentral gyrus responsible for activation of facial muscles. This area was localized in close proximity to surgical approach that required its intraoperative mapping. The identified zone corresponded to the data of preoperative fMRIs. Mapping data were incorporated into neuronavigation system. The area of facial muscle activation was marked by several points in navigation system (4 points on the periphery with activation and 3 points at a distance without activation).

According to biopsy data, diffuse astrocytoma (WHO Grade II) with increased proliferative potential was diagnosed.

Neuropsychologist examined a patient in postoperative period. Complex aphasia was revealed (efferent and afferent (parietal) motor and acoustic-mnestic (temporal) aphasia). Considering previous surgery on the left frontal lobe, we can think about damage to arcuate and upper longitudinal bundles (postoperative MR tractography was not performed).

The patient was discharged after 7 days. Considering features of tumor, clinical and radiological data, radiotherapy was recommended in 1—3 months after resection.

**MRI protocol**

fMRIs protocol (SignaHDxt, 3T) consisted of structural MR scans (3D T1-FSPGR BRAVO) and functional data based on fMRI with a motor (tapping test) (patient 1) and speech (word generation test) paradigm, viewing pictures, listening to the text with the same sequence of tasks (patient 2).

In case of rsfMRI, patients were instructed to keep eyes closed, remain relaxed, but not fall asleep and move as little as possible during scanning. Time of rsfMRI data registration was 12.5 min. Overall time of MRI was 40 min.

**Intraoperative neurophysiological mapping**

Surgical intervention in these two cases was performed under intraoperative electrophysiological monitoring. The second patient underwent awake craniotomy and ultrasound navigation-assisted procedure. This technique is successfully applied in our Center in patients with tumors of speech-dominant brain hemisphere.

Electrophysiological mapping implied direct cortical stimulation with analysis of motor zones (arms and legs) in the first patient and speech zones in the second one. Mapping data (coordinates of stimulation points) were incorporated into neuronavigation system. As a result, all points were divided into “positive” and “negative” in accordance with the presence or absence of activation.

Intraoperative speech monitoring was performed using a computerized “naming test” with nouns or verbs in response to simple non-color pictures (50 pictures depicting actions or objects). Automated series were also evaluated (counting from 1 to 10, listing months, days of a week). Free dialogue was held with a patient throughout awake resection of tumor if electrical stimulation was not performed (a patient was asked about the main stages of his life). Speech testing methods were selected depending on patient’s state upon awakening.

**fMRI data processing**

Intraoperative mapping, fMRIs and rsfMRI data were obtained. Preprocessing of the obtained functional MR data included several stages: importing data from MR scanner in DICOM format, bringing the anatomical and functional data to a single coordinate, and reducing movement-induced artifacts. Further, significant motion-induced artifacts were eliminated. Then, structural and functional data were compared using a data processing complex. At the next stage, rsfMRI data were analyzed using fmrirprep, GIFT Matlab software packages and MP signal decomposition into independent components (networks) (Constrained Independent component analysis, C-ICA).

Correlation of rsfMRI and fMRIs activation maps was evaluated using Dice coefficient. This coefficient characterizes overlapping of active voxels in both maps. Overlapping of rsfMRI and fMRIs activation maps was evaluated within pre-selected anatomical regions using standard masks of speech and motor cortex [6].

At the next stage, we analyzed coincidence of intraoperative data with rsfMRI and fMRIs activation zones. The number of both “positive” and “negative” points of intraoperative mapping was considered in immediate vicinity of activation zones.
Results

Comparison of localization of functional zones between fMRIs and rsfMRI

In the first patient, tapping-test (fMRIs) was followed by activation of precentral gyrus (motor zones of hands) and additional motor cortex (medial parts of frontal lobes) (Fig. 1). In rsfMRI, more extensive complexes of central gyri corresponding to bilateral motor and sensitive regions and additional motor regions were involved into activation of sensorimotor component (Fig. 1).

In the second patient, speech test in fMRIs (generating sentences with words, listening to the text) was followed by activation of inferior frontal gyrus in triangular part (Broca’s area), dorsal parts of superior temporal gyrus (auditory cortex and Wernicke’s area) and precentral gyrus in both hemispheres (areas of facial muscles). Bilateral activation of inferior, middle frontal gyri, temporal lobes, and lower parts of precentral gyri was noted in rsfMRI speech network (Fig. 2).

In the first patient, high degree of overlapping of fMRIs motor activation and rsfMRI sensorimotor was obtained (Dice coefficient 0.70). Activation areas corresponded to anatomical landmarks (complex of central gyri and additional motor zone).

In the second patient, low degree of overlapping of speech activation was noted (Broca’s area, Wernicke’s area, zone of facial muscles in fMRIs and rsfMRI speech network) (Dice coefficient 0.16). In our opinion, this may be due to greater individual variability of activation foci and their smaller dimension.

Comparison of localization of functional zones between fMRIs, rsfMRI and direct electrophysiological cortical stimulation

In the first patient, comparison of activation data for fMRIs and direct stimulation revealed that 3 out of 5 intraoperative “positive” points were localized within motor zone and 2 points at the border of motor zone. One point was localized at a small distance from activation zone (5 mm), that is an acceptable interpolation error. Thus, all 5 “positive points” were significantly localized within the activation zone.

Two out of 4 “negative” points were localized within motor activation area, 2 points — at the border of this area. Three out of 4 “negative” points were significantly localized within the activation zone.

Comparison of rsfMRI and direct stimulation data revealed that 3 out of 5 “positive” intraoperative points were localized within sensorimotor cortex, 2 points — at the border of this area including one point at acceptable distance (6 mm). Thus, all 5 “positive points” were significantly localized within the activation zone.

Analysis of “negative” points showed that 2 out of 4 points were localized on the border of activation zone, other 2 points — far from this area. No negative” points were localized within activation zone.

“Positive” and “negative” intraoperative points with motor activation of hands in two functional methods for a patient with glioblastoma of the left frontoparietal area are shown in Table 1 (patient 1).

In the second patient, comparison of activation data for fMRIs and direct stimulation revealed that 1 out of 4 “positive” point was in activation zone, 3 points — at an acceptable distance (7 mm). Two out of 4 “negative” points were localized within activation zone, 1 point — at the border of this zone, 1 point — at a distance from activation area. Comparison of rsfMRI and direct stimulation data revealed that 3 out of 4 “positive” points were localized at the border of activation zone (8–9 mm), one point — at a distance from this zone (12 mm). One out of 4 “negative” points was obtained at the border of activation zone, 3 points — at a distance from this area.

“Positive” and “negative” intraoperative points with articulatory activation of speech zone in two functional methods in a patient with astrocytoma of the left frontal-insular region are shown in Table 2.

Discussion

Clinical studies have identified the feasibility of rsfMRI in neurosurgical planning. However, our analysis of the published studies showed that rsfMRI is not clearly advisable for preoperative planning in patients with gliial tumors due to small sample size and no standardized approaches to data processing [5, 7, 8]. Nevertheless, some researchers have attempted to create tools for facilitating clinical implementation of rsfMRI in preoperative planning [9].

Currently, correspondence of functionally significant activation zones in fMRIs with detectable neural networks in rsfMRI is still important issue in the context of preoperative mapping. Intraoperative electrophysiological monitoring (direct electrical stimulation of sensorimotor and speech cortical zones) is essential for this problem. Moreover, craniotomy with awakening and full intraoperative contact with a patient are necessary to determine, for example, speech zone localization. Comparison of functional cortical zones before and during tumor resection is of great importance to minimize the risk of postoperative neurological complications. In this manuscript, we analyze two methods of functional MRI using independent components analysis (ICA), namely, with spatial limitations. This method ensures extracting of significant signal from rsfMRI (so-called neuronal resting state networks) without a parametric activation model. This approach is suitable for analysis of resting state and comparison of data of fMRI and direct intraoperative mapping of motor and speech zones in patients with brain glioma.
Discussion of our results is preceded by a small additional analysis of literature data in addition to the previously published review [2, 10].

S.M. Smith et al. (analysis of healthy volunteers) [6], D. Zhang et al. [11], T.M. Qiu et al. [12], P. Branco et al. [13], D. Dierker et al. [3], H.I. Sair et al. [4] (analysis of patients with brain tumors followed by motor and speech cortex lesion) reported good results on correspondence of functional architecture. So, S.M. Smith et al. identified the main activation networks via analysis of thousands of individual cards obtained from the BRAINMAP database. The authors identified resting state neuronal networks in 36 healthy volunteers, and these results had a clear correspondence between the identified networks and BRAINMAP maps. Thus, good coherence with known functionally significant cortical areas was observed [6].

D. Zhang et al. reported a differentiation of somatomotor cortex via resting state data analysis. Resting state functional mapping in 4 patients with tumors, including somatomotor cortex, showed localization of networks in those areas corresponding to cortical stimulation data. The authors concluded that comparison of neuronal networks using rsfMRI can improve specificity compared to fMRIs [11].

The differences between fMRIs and rsfMRI can have two completely different results. In this regard, it is also necessary to remember that cortical activation map in rsfMRI is different from fMRI, since these two functional methods are essentially different and measure different aspects of brain functions. fMRIs maps visualize activation only those brain areas involved into testing while rsfMRI mapping reflects all internal activity.

It is known that preoperative mapping of speech zones is associated with several methodological problems: variability of results in different speech paradigms (JR Binder et al. [14]), low quality of paradigm execution, motion-induced artifacts and low signal/noise ratio (D. Seixas and D. Lima [15]), and other components influencing an effectiveness of this method. As a result, specificity and sensitivity of classical fMRIs with assessment of speech zones are low compared to direct cortical stimulation [16]. G. Kuchcinski et al. (2015) reported sensitivity of fMRIs mapping for speech zones near 37.1% [17]. L. Junck et al. emphasize that fMRIs is “not
yet ready for adequate control” during glioma resection within speech zones [18].

H. I. Sair et al. (Johns Hopkins Hospital) believe that the first studies of speech cortex with rsfMRI were carried out in small samples of patients with brain tumors. These trials showed good agreement with fMRIs or direct stimulation. However, enlarged samples in recent studies were followed by significantly variable localization of speech zone activation [4]. So, J. Lu et al. analyzed 7 patients with gliomas. Sensitivity of rsfMRI in speech zone mapping was 87% only after expanding the radius of comparison of intraoperative points up to 1 cm. Primary sensitivity of rsfMRI was 60.9% [5]. In another study by P. Branco et al. based on ICA, correspondence between rsfMRI and fMRIs speech maps was analyzed in patients with brain lesions (tumors, epilepsy) [13]. As a result, a moderate correspondence between fMRIs and rsfMRI maps was found, especially in localized speech regions (mean Dice coefficient 0.248 throughout the brain).

In our research, correlation of data of both fMRI methods and intraoperative findings is defined in specified anatomical regions, unlike most studies with identification of activation of the entire brain. We also applied Dice coefficient to measure spatial similarity between the maps and obtained high correlation in the first patient (motor components) and low correlation in the second one (speech components). Considering clinical symptoms in the second patient, preoperative and intraoperative mapping data, we can assume changes in neural architecture caused by invasive diffuse growth of tumor. Identification of speech components is a more difficult task compared to sensorimotor ones, since speech zones have higher variability of localization. Moreover, these areas are associated with cognitive functions such as understanding, making, perception.

**Conclusion**

This report is devoted to rsfMRI-based analysis of functional neuronal activity influenced by various brain gliomas. In our opinion, rsfMRI-based analysis of individual changes in sensorimotor and speech neural networks may be valuable for preoperative non-invasive mapping of functional areas. Further studies aimed at im-

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*Fig. 2. MR scans in axial (a), sagittal (b) and frontal (d) planes in a patient with diffuse astrocytoma (WHO Grade II) of the left frontoinsular region.*

Combination of activation in fMRIs, rsfMRI and intraoperative responses. Enlarged fragment of the region of interest (c). fMRIs activation - red, rsfMRI — white, “positive” points — green, “negative” points — blue.
proving methodological approaches and instrumental technologies are required to implement this method in neurosurgical planning. Analysis of MRI data should be standardized and confirmed by intraoperative mapping.

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Authors’ participation:
Concept and design of the study — A.S.


Statistical analysis — T. M.-P., E.P.

Writing the text — A.S.

Editing — A.S.

The authors declare no conflicts of interest.

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Table 1. Correlation of intraoperative mapping data and sensorimotor cortex activation in fMRIs and rsfMRI (patient 1)

<table>
<thead>
<tr>
<th>Method</th>
<th>In activation zone</th>
<th>On the border (within 10 mm)</th>
<th>At a distance</th>
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<tr>
<td></td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>fMRIs</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>rsfMRI</td>
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<td>0</td>
<td>2</td>
</tr>
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Table 2. Correlation of intraoperative mapping and articulatory activation data in fMRIs and rsfMRI (patient 2)

<table>
<thead>
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<th>On the border (within 10 mm)</th>
<th>At a distance</th>
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<tr>
<td></td>
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<tr>
<td>fMRIs</td>
<td>1</td>
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<tr>
<td>rsfMRI</td>
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Short-term survival prediction scale in patients with metastatic brain disease caused by lung and breast cancer

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Abstract

Objective. To develop a prognostic scale suitable for distinguishing a group of poor prognosis with low survival prior to deciding on the appropriateness of radiotherapy.

Material and methods. We analyzed only those patients with reliably known date of death after previous WBRT to determine objective criteria allowing WBRT abandonment. WBRT was carried out in 100 patients with non-small cell lung cancer (n=49) and breast cancer (n=51) and confirmed metastatic brain disease. All procedures have been conducted at the radiotherapy department of the Herzen Moscow Oncology Research Institute since January 2014. The prescribed dose of 3 Gy was ensured in all patients. Total focal dose of 30 Gy delivered in 10 fractions was achieved in 77 cases, 36 Gy delivered in 12 fractions — in 23 cases.

Results. Death date was recorded in all patients (n=100) by January 2020. In the electronic SPSS database, death information was digitized for each patient up to 2–24 months, respectively. We identified eight the most significant factors by using of correlation analysis: primary tumor (controlled (0), uncontrolled (1)), number of brain metastases (<17 (0), ≥17 (1)), volume of brain metastases (<48 cm³ (0) ≥48 cm³ (1)), extracranial control (no metastases (0), metastases with positive dynamics after chemotherapy (1), continued growth after chemotherapy (2)), metastatic lesion of liver and lungs, respectively (no (0), yes (1)), functional status (≥70% (0), ≤ 60% (1)), carcinomatosis of the meninges (no (0), yes (1)). A simple summation of digital variables for factors 1—8 in each patient resulted a prognostic scale. Low risk of early mortality after WBRT was determined by 0—3 scores, intermediate risk — 4—5 scores, high risk — 6—9 scores. According to univariate analysis (log-rank 0.000), median survival rate varied in these groups: low risk — 15.5 months (11.4—19.7), intermediate risk — 5.26 months (4.6—6.0), high risk — only 1.35 months (0.9—1.8). Only 1 out of 15 high-risk patients (6—9 scores) survived 3 months (3.25 months). Inclusion of all eight factors into multivariate analysis revealed significant impact of only risk group on short-term survival. A 3-month survival in the high-risk group was 20.6 times lower (p=0.002) compared to the low and intermediate risk groups.

Conclusion. High significance of prognostic model and low informative value of each of the included factors emphasize the advisability of determining risk groups for short-term survival according to the suggested scale for each patient scheduled for WBRT. A simple assessment of separate predictors is pointless to decide whether WBRT is necessary.

Keywords: metastatic brain lesion, radiotherapy, prognosis scale.

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Abbreviations

KS — Karnofsky score
NSCLC — non-small cell lung cancer
TFD — total focal dose
CHT — chemotherapy
DS-GPA — diagnosis-specific GPA
GPA — Graded Prognostic Assessment
MS — median survival
QALY — quality-adjusted life-year
QUARTZ — quality of life after radiotherapy for brain metastases
RTOG — Radiation Therapy Oncology Group
WBRT — whole-brain radiotherapy
In a multiple-center study, median survival was calculated in 4259 patients with brain metastases and various primary cancers. Mean survival rate was less than 3 months in patients with lung cancer that was lower compared to breast, colon cancer and others [1].

After research by J. Horton et al., whole-brain radiation therapy (WBRT) has become a standard care for brain metastases. The authors performed distant ⁶⁷Co-therapy in combination with prednisone 40 mg daily (20 fractions with a single focal dose of 2 Gy, total focal dose 40 Gy). Actual survival time ranged from 3 days to 53 weeks. WBRT combined with prednisone ensured better survival rates, neurological and functional outcomes compared to prednisone alone [2].

Subsequently, WBRT in various fractionations did not show an improvement in survival and quality of life [3]. According to E.A. Barnes et al., a short course of WBRT with a prescribed dose of 4 Gy (5 fractions) was preferable for most patients with non-small cell lung cancer (NSCLC), as survival rates were comparable to prolonged WBRT programs [4].

To date, WBRT and concomitant dexamethasone therapy are widely used for brain metastases, including NSCLC. Potential benefits of WBRT are improved or stabilized neurological symptoms, improved quality of life and working capacity, reduced steroid doses. However, it is possible that the benefits of WBRT are overestimated due to possible neurological deterioration. WBRT-associated toxicity includes hair loss, headache, nausea, weakness and fatigue, while potential benefits of WBRT may come from small pilot studies [4].

According to the National Comprehensive Cancer Network guidelines (NCCN guidelines, version 1.2012, USA), WBRT doses can vary from 20 to 40 Gy (5—20 fractions) for breast cancer. The standard schemes are 10 fractions with a single dose of 3 Gy and 15 fractions with SFD of 2.5 Gy [5]. The recommendations have not changed in future versions (NCCN Guidelines Central Nervous System Cancers, Version 2.2018).

It should be noted that there were no randomized clinical trials confirming an improvement of quality of life and overall survival after WBRT. An updated review published in an electronic database of evidence-based medicine in 2012 included randomized controlled trials of phase III (54 trials) for brain metastases. None of the studies with modified WBRT fractionation schemes showed any advantages compared to standard treatment [6].

Back in 2006, M.N. Tsao et al. noted the need to analyze an effectiveness of WBRT for brain metastases compared to symptomatic therapy [7]. The UK Clinical Research Division under support of the National Committee and the Cancer Research Institute initiated a randomized Phase III QUARTZ study (quality of life after radiotherapy for brain metastases). In this trial, the authors sought to establish whether WBRT can be avoided for brain metastases. Another purpose was analysis of survival and quality of life if WBRT is rejected. Patients with NSCLC and brain metastases who were denied in microsurgical intervention and stereotactic radiotherapy were randomized into 2 groups (1:1). In the first group, therapy included dexamethasone and WBRT (20 Gy for 5 daily fractions). In the second group, symptomatic therapy included only dexamethasone. The dose of dexamethasone was determined by intensity of symptoms and reduced in case of regression of symptoms. The main evaluation criterion was quality-adjusted life-year (QALY). Patients filled the EQ-5D questionnaire weekly. Additional drug treatment (chemotherapy) was not carried out. According to interim data (2013), no deterioration in quality of life, overall survival and QALY was observed if WBRT was not performed. However, the experts decided to continue this trial [8].

For the period from March 2, 2007 to August 29, 2014, 538 patients were selected from 69 British and 3 Australian centers. They were divided into supportive therapy + WBRT group (269) or isolated supportive therapy group (269). Stratification included Karnofsky score, gender, metastatic brain lesion and primary focus. Baseline characteristics were similar in both groups, mean age was 66 years (range 38—85). Patients with low functional status prevailed (Karnofsky score≤60). Incidence of drowsiness, hair loss, nausea, dryness or itching of head skin was higher after WBRT. At the same time, there were no differences in the incidence of severe adverse events between both groups. Overall survival rate and quality of life were similar. In the QUARTZ trial, MS after radiation therapy was only 64.4 days. Moderate advantages in QALY values (questionnaire) in favor of OSC + WBRT and similar survival and quality of life in both groups did not exclude the feasibility of WBRT [9].

However, the role of WBRT in patients with NSCLC followed by brain metastases has been called into question after publication of QUARTZ results. Obviously, there is a group of patients with brain metastases who have extremely low survival and do not benefit from WBRT. Considering the side effects of radiotherapy, WBRT is not advisable in the last few weeks of life if drug therapy and dexamethasone result similar outcomes. However, there are still no reliable criteria for identifying patients with useless radiotherapy. At the same time, according to multiple pilot studies, a significant number of patients have better survival compared to the QUARTZ trial data. Thus, it is difficult to extrapolate the results of this research [10]. Moreover, further development of systemic therapy [11], including recent advances in immunotherapy [12], suggests that longer life expectancy can be expected. The purpose of some studies was the development of a prognostic model for identifying the groups with low survival. Most of them were performed to select patients for surgical treatment or stereotactic radiotherapy. In 1997, RTOG (Radiation Therapy Oncology Group) proposed RPA classification after analysis of various parameters in 1200 patients with brain metastases in three studies.
(1979—1993). Based on this analysis, three classes of patients were identified [13]:

- class 1: patients with KS ≥ 70, age <65 years and controlled primary tumor without extracranial metastases (median survival 7.1 months);
- class 3: patients with KS < 70 (median survival 2.3 months);
- class 2: all other patients (median survival 4.2 months).

After 10 years, RTOG proposed a new prognostic index for patients with brain metastases — Graded Prognostic Assessment (GPA) [14]. C. Nieder et al. retrospectively analyzed survival of 124 patients with brain metastases (only one third had NSCLC). All patients had low GPA or DS-GPA (diagnosis-specific graded prognostic assessment score) (0—1.5 scores). Regardless of total score, DS-GPA alone did not become a satisfactory prognostic factor. Nevertheless, a subgroup of 63 (51%) patients with short survival was distinguished regardless of treatment strategy. These are patients with GPA score 0—1.5, age ≥ 75 years, KS ≤ 50, uncontrolled primary tumor and extracranial metastases into at least two organs [15].

Initially, DS-GPA index was based on 4 factors identified after analysis of survival of 1833 patients with NSCLC and brain metastases for the period 1985—2005. These factors were age, KS, extracranial spread and number of brain metastases [14]. MS was 7 months since brain lesion treatment onset. Data of 2186 patients with NSCLC for the period from 2006 to 2014 were additionally analyzed to develop an updated Lung-molGPA model. Two new factors were determined as significant predictors in addition to 4 factors of DS-GPA index. These are mutational status of EGFR and ALK in patients with adenocarcinoma. MS in this study was 12 months, in patients with NSCLC (adenocarcinoma) and Lung-molGPA index 3.5—4.0 — almost 4 years [16].

However, prognostic value of DS-GPA and Lung-molGPA models remains uncertain, especially for patients with different molecular types. MS in patients with NSCLC (n=1184) was 14.0 months after diagnosis of metastatic brain lesion. Both models were effective in predicting overall survival (p<0.001). Lung-molGPA model ensured more accurate prognosis in patients with mutant genotype. However, prognosis was not successful in patients with “wild” type (p=0.133) [17].

C. Nieder et al. analyzed the Lung-molGPA predictive model in a retrospective trial of 269 German and Norwegian patients. The authors confirmed high accuracy of this classification. MS was 3.0, 6.2, 14.7 and 25.0 months in 4 different prognostic groups of patients with pulmonary adenocarcinoma, respectively. For other forms of NSCLC, these values were 2.4, 5.5 and 12.5 months, respectively [18].

Several prognostic models have been developed for breast cancer with brain metastases. In addition to age, tumor subtype and KS (Breast-GPA), a number of brain metastases (Modified Breast-GPA) was added [19]. Clinical data of 668 patients in four facilities were analyzed for the period from 1996 to 2016. Patients were classified using Breast-GPA and Modified Breast-GPA systems. Overall survival was determined from the time of diagnosis to death or the last follow-up. Both models accurately predicted survival (p<0.001 for both indicators), while an effectiveness of Modified Breast-GPA model was higher [20].

Thus, we can assume that no specific factors to refuse WBRT are determined.

The purpose of the study was to develop a prognostic scale ensuring selection of patients with unfavorable prognosis and low survival rate before administration of radiotherapy.

We attempted to create a prognostic scale for selection of patients with unfavorable prognosis before deciding on the appropriateness of radiotherapy. A fundamentally new approach has been applied. Thus, only those patients with known date of death after previous WBRT were included in the study. Nosological forms included NSCLC and breast cancer.

### Material and methods

To search for objective criteria for rejecting WBRT, we enrolled only those patients with known date of death after previous WBRT. WBRT has been administered in patients (n=100) with NSCLC (n=49) and breast cancer (n=51) followed by brain metastases. Irradiation has been carried out at the radiotherapy department of the Herzen Moscow Cancer Research Institute since January 2014. Men made up 29% in the total cohort of patients. In all patients, KS was assessed before microsurgical intervention or dexamethasone therapy and before radiotherapy.

Microsurgical treatment for symptomatic metastases was performed in 33 out of 100 patients. One-line chemotherapy was carried out in 31 patients, two-line — 22 patients, several-line — 20 patients. Chemotherapy was not performed in 27 patients. WBRT was followed by special drug treatment in 68 patients. Targeted therapy was used in 29 patients at various stages.

An uncontrolled local process (no resection of primary tumor or local continued growth) was observed in 40 patients. Solitary brain lesion was detected in 18% of cases, several metastases — in 14%, multiple metastases — in 68% of cases (4—10 in 40%, 11—55 in 28%). The number of metastases ranged from 1 to 55 (median 6, 95% CI 5—8). Metastatic brain lesion volume ranged from 1.148 to 181.83 cm³ (median 14.856, 95% CI 12.32—18.85). In 11 patients, volume of lesion was over 48 cm³. Uncontrolled extracranial process was noted in 40% of cases, controlled process — in 28%, no extracranial metastases — in 32% of patients. Metastatic liver lesion was recorded in 21 patients, lung metastases — in 34% of cases. Minimal KS ≤ 60 prior to treatment was observed in 32% of cases, before WBRT — in 12%.
Carcinomatosis of brain meninges was recorded in 18% of patients, dislocation of midline structure ranged from 0 to 17 mm (mean 2.45 mm, 95% CI 1.64–3.26).

Radiotherapy was carried out on linear accelerators with equipment level 3 in 32% of cases, level 2 — 51%, gamma therapy (level 1) — 17% of cases. The prescribed dose of 3 Gy was used in all patients. Treatment program with 10 fractions up to total focal dose of 30 Gy was carried out in 77 patients, 12 fractions up to total focal dose of 36 Gy — in 23 patients.

Scheduled irradiation was determined as:
- GTV — gross tumor volume, all metastases were obligatory contoured;
- CTV — clinical target volume including the entire volume of brain along the internal bone structures (GTV is less than CTV);
- PTV (planning target volume) — CTV plus 5 mm to capture the affected area in case of meningeal carcinomatosis;
- the prescribed dose was calculated in accordance with 100% isodose, while 90% of CTV was supposed to cover V90 (2.7 Gy);
- considering localization of tumor, we outlined the normal functionally significant brain structures.

Cox regression survival model and Kaplan — Meier method, correlation analysis and other programs were used to analyze treatment outcomes.

**Results**

The dates of deaths have been recorded in all 100 patients by January 2020. In the electronic SPSS database, death information for each patient is digitized up to 2—24 months after radiotherapy onset (Fig. 1).

We used standard correlation analysis and determined eight the most significant predictors of mortality within 2—6 months (early death) after radiotherapy:

1. Primary focus.
2. Number of brain metastases.
3. Volume of brain metastases.
4. Extracranial control.
5. Metastatic liver lesion.
7. Minimal KS before the appointment of dexamethasone or microsurgical intervention.
8. Carcinomatosis of brain sheaths.

For the 1st factor (controlled (0) or not controlled (1) primary focus), moderate correlation with mortality ≥ 6 months was observed ($r=0.302; p=0.002$), no significant differences were noted for earlier mortality ($p>0.05$).

For the 2nd factor (<17 brain metastases (0) or ≥ 17 brain metastases (1)), weak correlation with 3-month mortality was noted ($r=0.239; p=0.017$).

For the 3rd factor (brain metastases volume <48 cm$^3$ (0) or ≥48 cm$^3$ (1)), weak correlation with 2-month ($r=0.210; p=0.036$) and 6-month mortality ($r=0.231; p=0.021$) was observed.

For the 4th factor (no extracranial metastases (0), involution of metastases under chemotherapy (1), growth under chemotherapy (2)), moderate correlation with 2-month ($r=0.325; p=0.001$), 3-month ($r=0.370; p=0.000$) and 6-month mortality was found ($r=0.381; p=0.000$).

For the 5th factor (absence (0) or presence (1) of metastatic liver lesion), moderate correlation with 2-month ($r=0.402; p=0.000$) and 3-month mortality ($r=0.418; p=0.000$) was observed. Moreover, there was weak correlation with 6-month mortality ($r=0.231; p=0.021$).

For the 6th factor (absence (0) or presence (1) of metastatic lung lesion), weak correlation with 2-month mortality ($r=0.231; p=0.021$) and moderate correlation with 3-month ($r=0.410; p=0.000$) and 6-month mortality was observed ($r=0.352; p=0.000$).

For the 7th factor (KS ≥ 70 (0) or ≤ 60 (1)), moderate correlation with 2-month ($r=0.312; p=0.002$), 3-month ($r=0.338; p=0.001$) and 6-month mortality was observed ($r=0.357; p=0.000$).

For the 8th factor (absence (0) or presence (1) of meningeal carcinomatosis), weak correlation with 2-month ($r=0.241; p=0.016$), 3-month ($r=0.239; p=0.017$) and 6-month mortality was noted ($r=0.218; p=0.030$).

A simple summation of digital indicators for factors 1—8 in each patient resulted a prognostic scale (0—3 points — low risk, 4—5 points — intermediate risk, 6—9 points — high risk of early mortality after WBRT).

Correlation is increased sharply for the proposed prognostic scale (2-month ($r=0.553; p=0.000$), 3-month ($r=0.615 — strong; p=0.000$) and 6-month ($r=0.502; p=0.000$) mortality).

According to univariate analysis (Log Rank 0.000), MS was different in the prognostic groups: 15.5 months for low risk (95% CI 11.4—19.7), 5.26 months for intermediate risk (95% CI 4.6—6.0), 1.35 months for high risk (95% CI 0.9—1.8) (Fig. 2).

Only 1 out of 15 high-risk patients (6—9 points) survived 3 months (3.25 months). The probability of death within 3 months after WBRT was estimated using Cox regression survival model (multivariate analysis). Survival curves are shown in Fig. 3.

It should be noted that only risk group significantly influenced short-term survival after forced inclusion of prognostic parameters and each of the 8 previously described factors into multivariate model. Three-month survival was 20.6 times lower in the high-risk group ($p=0.002$) compared to the low and intermediate risk groups (Table).

High statistical significance of the parameters of prognostic model and low informative value of separate factors emphasize advisability of determining the risk group of short-term survival for each patient eligible for WBRT. A simple assessment of multiple predictors to decide whether WBRT is necessary is pointless.
Discussion

Considering current literature data, there are no well-founded recommendations determining feasibility of WBRT or isolated therapy in patients with NSCLC and breast cancer followed by metastatic brain lesion. We developed a scoring system for analysis of short-term mortality risk. This model allowed us to determine a group of patients with inappropriate WBRT since MS is only 1.35 months in these patients (95% CI 0.9—1.8).

However, the prognostic scale has another applied value. Radiologist can apply more aggressive approaches of radiotherapy in low risk (0–3 points) patients. First of all, it concerns an improved local control over brain metastases using radiation boost. Our data confirm the feasibility of such treatment (Fig. 4).

According to univariate analysis, MS was 25.0 and 12.2 months in the groups of WBRT and subsequent radiation boost (n=39) and isolated WBRT (n=39), respectively (Log Rank 0.004, Breslow 0.000).

Conclusion

The proposed and mathematically justified prognostic scale is valuable to optimize treatment of patients with non-small cell lung cancer and breast cancer followed by brain metastases. Patients with low risk of early mortality after radiotherapy are candidates for boost. The last one may be performed immediately after the first stage of WBRT or in long-term period.

Patients with intermediate risk of early mortality after radiotherapy are not candidates for irradiation boost after WBRT. The last one may be carried out only in patients with favorable course of cancer in long-term after WBRT.

Advisability of WBRT is doubtful in patients with high risk of early mortality after irradiation. An alternative is concomitant therapy with inclusion of dexamethasone into treatment regimen.

Authors’ participation:

Concept and design of the study — P.D.
Collection and analysis of data — P.D., A.B., V.G.
Statistical analysis — P.D., A.B., V.G.
Writing the text — P.D., V.G.
Editing — P.D., V.G.

The authors declare no conflicts of interest.

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Fig. 1. SPSS electronic database with digitization of mortality data up to 2, 3, 4, 5, 6, 12, 18, 24 months, respectively.
Odds ratio for prognostic scale parameters and eight factors in multivariate analysis in assessing the probability of fatal outcome within 3 months after WBRT

<table>
<thead>
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<th>Odds ratio</th>
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Fig. 2. Survival curves for various risk groups.

Fig. 3. Three-month survival curves for various risk groups.

Fig. 4. Survival curves depending on radiotherapy mode in patients with low risk of short-term mortality.
The manuscript is devoted to an urgent medical problem—whole-brain radiotherapy in patients with brain metastases of non-small cell lung cancer (NSCLC) and breast cancer (BC). This is especially important since irradiation paradigm for patients with brain metastases is being changed towards local exposure.

Thus, reappraisal of the role of WBRT in the treatment of these patients is required. According to the guidelines of the National Comprehensive Cancer Network [1], stereotactic radiotherapy is preferred in patients with localized brain metastases if extracranial metastases are stabilized or reserved of systemic treatment are.

REFERENCES


available. Similar recommendations are contained in other modern guidelines for irradiation of brain metastases [2, 3].

WBRT is currently preferred in patients with high risk of distant metastases de novo (with low functional status and multiple brain metastases as a rule), leptomeningeal and severe extracranial lesion.

Until recently, one of the indications for WBRT was widespread extracranial metastases, no reserves for drug treatment and low functional status. QUARTZ randomized trial (phase III) [4] was devoted to analysis of exclusion of WBRT in patients with brain metastases of non-small cell lung cancer if neurosurgery or radiosurgery is impossible. Thus, this research showed no differences in overall survival and quality of life in patients scheduled for drug therapy alone compared to those who underwent WBRT and drug therapy. This fact made it possible to determine a group of patients with brain metastases of NSCLC and potentially inadmissible WBRT considering similar overall survival under drug therapy alone.

In this manuscript, the authors attempted to more clearly characterize a group of patients with brain metastases of NSCLC and breast cancer in whom WBRT is not advisable, since irradiation does not increase their overall survival. The authors analyzed treatment outcomes in 100 patients with brain metastases of NSCLC and breast cancer, who underwent WBRT at the radiotherapy department of the Herzen Moscow Cancer Research Institute. As a result, they developed a mortality prediction scale for patients with brain metastases undergoing WBRT. Thus, a group of high-risk patients with impractical WBRT was determined considering median overall survival near 1.35 months (95% CI 0.9—1.8). The authors emphasize an importance of intensified irradiation in intermediate and low risk patients with brain metastases considering improved overall survival in case of WBRT combined with irradiation boost.

There are comments on the writing style of the article, because sometimes you have to guess what idea the author tried to reflect in certain sentences. This situation is compounded by numerous foreign abbreviations. In our opinion, it is reasonable to avoid multiple foreign abbreviations in Russian-language articles.

There are questions to statistical methods used in this research. For example, is it rational to compare the factors and the scale based on these factors in multivariate analysis? Moreover, what for it is necessary? Obviously, prognosis cannot depend on only one factor. Therefore, significance of various factors is initially assessed in univariate analysis and their significance is analyzed in multivariate analysis. Prognostic scale is created at the last stage. It is a final goal that does not require comparison with any factors in multivariate analysis. You can test a scale in prospective trial, but that's another matter. Why was multivariate analysis with forced inclusion of variables used rather sequential exclusion of variables “forward” or “backward”?

There are some controversial claims in the manuscript. For example, the authors say that “whole-brain irradiation can result in an improvement of quality of life”, although the opposite findings are known from the literature and clinical practice. A statement of “improved overall survival in patients with brain metastases after irradiation boost” should be based on clear data about comparable groups of WBRT and WBRT + boost (clinical parameters, extracranial lesion, therapeutic approach, clinical response, etc.). Otherwise, this is only an assumption that this treatment option may be effective in some cohort of patients.

Obviously, it is necessary to continue this research and to show what prognostic factors are more often observed in different prognostic groups. It is desirable to characterize a group of patients with localized brain metastases (32% of the analyzed patients). Indeed, it is not clear why was WBRT preferred over stereotactic radiotherapy in this group exactly? Patients with low risk of early mortality after radiotherapy are also interesting, since some patients in this group are also likely to be candidates for stereotactic radiotherapy.

Undoubtedly, this manuscript is extremely important and necessary in our country. An experience of the Herzen Moscow Cancer Research Institute as one of the largest oncological institutions is extremely important for improving own treatment results and comparative assessment of the work of various radiotherapy departments.

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REFERENCES


Clinical, structural and functional features of paroxismal syndrome in insular and temporal lobe tumors

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Abstract

Objective. To analyze the characteristics of paroxysmal syndrome in insular and temporal lobe tumors, to determine their relationship with the histological structure of tumor, to assess the effect of tumor growth nature on severity of disease.

Material and methods. A retrospective analysis enrolled 80 patients aged 11 — 80 years with insular and temporal lobe tumors and symptomatic epilepsy. All patients underwent surgery at the Polenov National Research Neurosurgery Center in Almazov National Medical Research Center for the period from 2012 to 2018.

Results. The main group consisted of 29 patients with tumors of temporal and insular lobes. Control group of 51 patients with temporal gliomas was formed for comparative analysis. It was found that involvement of insular lobe into paroxysmal syndrome is characterized by attacks with a motor component, somatosensory paroxysms, vegetative manifestations (respiratory attacks, salivation, nausea), speech disorders and taste hallucinations. Derealization, motor arrest and déjà vu/jamis vu paroxysms were more common in patients with temporal lobe lesion. Neoplastic lesion of the insular lobe shortens the period between manifestation of paroxysms and surgical treatment. Moreover, this type of disease is characterized by higher incidence of seizures compared to isolated temporal lobe tumors.

Keywords: insular epilepsy, temporal lobe epilepsy, insular glioma, epilepsy surgery.

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Abbreviations

BN — benign neoplasms
MN — malignant neoplasms
MRI — magnetic resonance imaging
Epileptic seizures associated with brain tumors make up 6—10% of all cases of epilepsy and 12% of cases of symptomatic epilepsy. Astrocytic gliomas, gangliogliomas and dysembryoplastic tumors are most often associated with epileptic syndrome [1]. Pathogenesis of epilepsy in brain tumors depends on various factors including histological type of the tumor, its localization and changes in perifocal brain matter [1].

Insular tumors account for approximately 25% of all low-grade gliomas and 10% of high-grade gliomas [2—4]. These tumors manifest with epileptic seizures in about 80% of cases [4—6]. It is known that seizures disappear after resection of insular glioma in 65—90% of cases [2, 3, 6—11]. There is a reason to believe that analysis of structural and functional organization of paroxysmal disorders in patients with insular tumors will provide the new data on the pathogenesis, diagnosis and treatment of symptomatic epilepsy associated with lesion of the insular lobe.

The purposes of the study were to analyze the paroxysmal disorders associated with tumors of insular and temporal lobes depending on the biological and histological nature and growth of tumor, to assess the effect of tumor growth type on the course of disease.

Material and methods

A retrospective analysis included 80 patients with tumors of the temporal and insular lobes who underwent surgical treatment at the neurosurgical department No. 4 and the department of pediatric neurosurgery of the Polenov Russian Research Institute of Neurosurgery for the period from 2012 to 2018.

Inclusion criteria were neoplasms of insular and temporal lobes and paroxysmal disorders.

Preoperative examination included:

• anamnestic analysis (age of the onset of disease, semiology of seizures, their frequency and severity);
• electrophysiological studies (electroencephalography, video electroencephalography, electrocorticography);
• neuroimaging (magnetic resonance imaging (MRI) 1.5 T, methionine and 18F-FDG positron emission tomography).

Semiology of seizures was analyzed in accordance with the classification of the International League Against Epilepsy [12]. Tumors were classified according to the recommendations of the World Health Organization (WHO) [13].

Statistical analysis was carried out using STATISTICA 12 software package. Descriptive data are presented mainly as median (minimum — maximum). Between-group comparison was performed by using of Mann – Whitney test and F-test for the difference of variances, normal distribution was assessed using Kolmogorov–Smirnov test. Predictors were analyzed by using of correlation analysis. Kaplan — Meyer curves were used to analyze freedom from surgery.

Results

There were 41 (51%) women among 80 patients. Mean age of patients was 40 (13—79) years, mean age at the first seizures — 35 (1—74) years. In addition to epileptic seizures (as inclusion criterion), headache was the second most common symptom (51%). Preoperative Karnofsky/Lansky score 70—80 was observed in 71 (89%) patients, <60 points — in 9 cases (11%). Neurological deficit included cognitive impairment in 43 (53%) patients, paresis in 13 (16%), speech impairment in 6 (7%) cases and visual impairment (diplopia, loss of visual fields) in 5 (6%) patients. MRI found malignant lesion of the insular lobe in 27 (34%) cases. Positron emission tomography was performed in 22 patients. Foci of hypometabolism and accumulation of radiopharmaceutical in the insular lobe were noted in 8 (36%) patients. According to EEG data, paroxysmal activity in temporal leads was recorded in 39% of patients, frontotemporal leads — 15%, posterior occipital leads — 6% (Fig. 1—6).

A group of patients (n=29) with structural lesion of the insular lobe (main group) was identified after analysis of imaging data and intraoperative morphometry. There were 10 (35%) men and 19 (65%) women in this group. Mean age of patients was 41 (11—79) years. Tumor of the right hemisphere was diagnosed in 17 (59%) cases, dominant left hemisphere — in 12 (41%) cases. The control group (n=51) consisted of patients with temporal lobe tumor (28 (55%) men). Mean age was 40 (13—79) years. In this group, tumor of the right hemisphere was diagnosed in 30 (58.8%) patients, left hemisphere — 21 (41.2%) patients. In the main group, malignant neoplasms were detected in 18 (62%) patients, benign neoplasms — in 11 (38%) cases. In the control group, incidence of malignant and benign tumors was similar (26 (51%) and 25 (49%) cases, respectively).

In the main group, duration of disease until surgery was 23 (1—156) months, in the control group — 24 (1—396) months (p=0.4; Mann — Whitney test) (Fig. 7). This value was less than 3 years in the majority (70%) of patients with insular lobe lesion. Patients aged over 30 years made up 67% by the moment of clinical manifestation (mean age 40 (1—77) years). Earlier onset of disease was observed in 27% of patients in the control group (mean age 34 (1—78) years) (Fig. 7).

Incidence of epileptic seizures ranged from a few per year up to 10 per day. Daily paroxysms were observed in 36% of patients. In the main group, patients with frequent (1 or more times a day) seizures prevailed (48%). In 5 (17%) patients, seizures were rare (several times a year). In 10 (35%) patients, paroxysms recur several times a month. In the control group, patients with rare (less than 1 paroxysm a week) seizures prevailed (72.5%) (Fig. 8; p=0.017, Mann-Whitney test).

Aura with fear, olfactory and taste hallucinations was described by 5 (17%) patients with insular glioma. There was a positive correlation between the aura and large tu-
mors ($r=0.60$). In the control group, aura was observed in 10 (20%) patients, and reverse correlation was revealed ($r=-0.16$). Thus, between-group analysis revealed higher incidence of aura in patients with smaller tumors.

In 58% of cases, there was a combination of 2–4 types of paroxysms (4 types — 2.5%, 3 types — 10%, 2 types — 45%, 1 type — 42.5%). Seizure polymorphism and the complexity of ictal manifestations were observed in the main group. Most patients ($n=23$, 79%) had focal seizures, 6 (21%) patients — focal seizures followed by bilateral tonic-clonic attacks. In the control group, focal seizures followed by bilateral attacks were observed in 23 (45%) patients. There were no patients with primary generalized seizures.

Somatosensory crisis was the most common form of paroxysms in patients with insular lobe lesion ($n=14$, 48%). This paroxysm included a sensation of “internal heat”, goosebumps and/or something burning in the limbs, numbness of the lips, corner of the mouth. Daily seizures were diagnosed in 54% of cases. All symptoms were contralateral to the lesion side. Similar paroxysms were noted in 5 patients with BN and 9 patients with MN (Fig. 9). In the control group, somatosensory paroxysms were revealed in 7 (14%) patients. Patients described these seizures as tingling or numbness of the limbs. However, the area of these sensations was much wider. Somatosensory paroxysms were rare and occurred several times a year. These disorders were more common in patients with BN (67%). Taste and olfactory hallucinations were detected in 10 (35%) patients with temporal lobe and insular tumor (olfactory disorders — 3 patients, taste hallucinations — 7 patients). These paroxysms were not combined in the same patient. According to qualitative analysis, all of the above-mentioned paroxysms were negative and described as “smell of gasoline”, “something burning”, “taste of something sour”. Incidence of these paroxysms was similar and did not depend on histological structure of tumor. Daily hallucinations were noted in half of cases. In the control group, olfactory hallucinations were more common ($n=16$, 31%). Taste paroxysms were less common (8%) in patients with BN unlike olfactory disorders. Motor component of seizure including fasciculations of the arm or facial muscles was observed in 8 (28%) patients of the main group. These seizures recurred daily in 88% of cases. In 7 (88%) patients, the tumor was malignant. Motor component of seizure was less common in the control group. Three (6%) patients had clonic convulsions in the limbs. In 2 (67%) patients with malignant tumor, seizures occurred daily.

Vegetative component including epigastric ascending sensations, respiratory symptoms (“lump in the throat, spasm”), nausea and skin hyperemia was observed in 7 (24%) patients of the main group. Salivation associated with seizure was noted in 2 patients with temporal and insular lobe malignancy. Four (8%) patients with temporal lobe glioma described a “feeling of heaviness behind the sternum” and “dry throat”. Derealization disorder was observed in 6 (21%) patients with insular glioma, emotional paroxysms (fear and anxiety) — in 7 (24%) patients.

Ictal speech impairment was detected in 2 (7%) patients with insular tumor. Ictal speech disorders (motor and sensory aphasia) were observed in 4 (8%) patients with dominant hemisphere tumor in the control group. Emotional paroxysms (unmotivated fear, anxiety) occurred in 5 (10%) patients. Postictal motor and speech deficiency, disorientation were recorded in 4 patients of the main group and in 6 patients of the control group.

In the main group, postictal deficit was more common in patients with lesion of the non-dominant hemisphere. Similar correlation was absent in the control group. However, we found a correlation between the likelihood of postictal deficit and duration of disease ($r=0.39$), motor manifestations of seizures ($r=0.38$) and permanent speech deficiency ($r=0.43$).

Twenty out of 80 patients have previously undergone surgery. Therefore, we could determine the true dimensions of tumors only in 60 patients.

According to neuroimaging data analysis, the main group was characterized by more compact localization of tumor (mean 100 cm³) (Fig. 10). In the control group, neoplastic process was not compact, dispersion of dimensions was disproportionate ($p=0.019$, F-test for variance comparison). There were significant differences in Kaplan — Meier estimator for the endpoint of disease ($p=0.031$, Cox F-test; Fig. 11). The bifurcation point of both Kaplan — Meier curves corresponds to the median and is approximately 8—9 months.
Discussion

Insula is an isolated brain lobe and one of the higher centers of autonomic nervous system [14, 15]. Isolated insular epilepsy is a rare phenomenon and usually discussed as a part of temporal lobe epilepsy plus [16]. In our study, clinical manifestation in the form of epileptic seizures is usually associated with isolated lesion of temporal lobe or combined lesion of temporal and insular lobes.

We have analyzed MRI-negative temporal lobe epilepsy at the City Epileptological Center and revealed clinical signs of insular lesion in 14.5% of patients with seizures [17]. According to our data, tumor-induced insular lobe lesion is observed in 37% of patients with temporal lobe neoplasm followed by epileptic seizures. Other authors reported insular lobe lesion in 25—85% of cases [2—6, 8].

Insula is one of the most epileptogenic brain lobe. Insular gliomas result paroxysmal disorders as predominant clinical symptoms in 70—80% of patients [2—6, 8]. It is known that paroxysms following insular cortical stimulation are similar to temporal and parietal seizures [7, 18—21]. According to our data, the structure of paroxysmal disorders following temporal and insular lobe tumors differs from isolated temporal lobe epilepsy.

Fig. 2. Epileptiform activity in the left frontotemporal leads in a 61-year-old patient with glioblastoma of the left temporal lobe (Fig. 1).

Fig. 3. MRI, T1WI. Glioblastoma of the right temporal and insular lobes (a 28-year-old patient S.).

The first feature is high incidence of focal sensory disorders in perioral region and spread to the upper limb.
Similar attacks occurred in 48% of cases. In most cases, neuroimaging revealed a tumor affecting posterior insular cortex. Seizures in the form of ascending undulating sensation (unpleasant wave of “heat”) were especially typical for insular epileptic paroxysms. Similar complaints were noted in all 4 patients with MN. These data are consistent with the results of other researchers [10, 18–20, 22, 23].

Vegetative manifestations are also typical for insular paroxysms. Vegetative paroxysms and taste hallucinations are common in case of lesion of anterior part of the insular cortex [22, 24]. In contrast to epigastric paroxysms following temporal lobe epilepsy, crises in patients with insular lobe gliomas were distinguished by severe manifestations, multiple components, and accompanied by salivation and nausea. T. Blauwbomme et al. (2013) revealed a vegetative epigastric component in 47% of patients [22]. N. Catenoix et al. (2008) described the paroxysms with ictal vomiting in patients with anterior insula lesion [25]. S.M. Oppenheimer et al. (1992) observed heart rate and blood pressure changes during insular cortex irritation in 50% of cases [14].

Taste hallucinations occurred in 24% of patients with insular lesion. According to N. Fukuda et al. (1991), insula and anterior opercular area are the primary taste cortical centers [26]. S. B. Buklina et al. (2016) found olfacto-
ant, metallic” taste hallucinations during stimulation of central insular cortex [28].

The role of the insula in speech function was first established in patients after previous cerebrovascular accident and ischemic lesion of the insular lobe. Dysarthria or speech apraxia were observed in these patients [15]. N.F. Donkers (1996), A. Afif et al. (2010) showed that lesion of anterior parts of the left insula results speech planning disorders [23, 29]. In our study, speech disorders (arrest

Fig. 6. Epileptiform activity in the left temporal leads in a 48-year-old patient with anaplastic ganglioglioma of the left temporal and insular lobes (Fig. 5).

Fig. 7. Age of patients at the time of clinical manifestation and surgical treatment (hereinafter: O — insula).

Fig. 8. Incidence of epileptic seizures in all groups. 0 — several times a year, 1 — monthly, 2 — several times a month, 3 — weekly, 4 — daily.
of speech or dysarthria) occurred in 2 (7%) patients with lesion of anterior and posterior parts of the insula.

Motor seizures occurred in 8 (27%) patients. According to the literature data, motor manifestations in the structure of insular paroxysms occur in 20—100% of cases. These disorders are more common in case of stimulation of anterior part of the insular cortex [18, 23, 28, 30]. This is explained by the probable spread of epileptic activity towards adjacent opercular region and frontal lobe [18]. However, A. Afif et al. (2010) analyzed the anatomical and functional organization of the insular lobe and revealed that the areas responsible for motor and sensory paroxysms under stimulation are closely localized. These data indicate a somatotopic representation of these functions [23]. In our sample, motor paroxysms were usually combined with vegeto-visceral (87.5%) and somatosensory (70%) manifestations that also indicates central (middle) localization of motor centers in the insular cortex.

We have analyzed chronological features of insular lobe epilepsy. For this purpose, we have compared the paroxysms at the onset of disease and seizures at the time of examination. In the main group, mean duration of disease was 23 (1–156) months. It has been established that progression of disease and diffuse epileptic changes in the insular cortex are accompanied by more complex structure of seizures. Incidence of paroxysmal disorders is increased approximately by 1.5 times. In our study, incidence of paroxysmal seizures in insular lobe epilepsy was higher compared to temporal lobe epilepsy. Moreover, these seizures were focal without impaired consciousness.

**Conclusion**

Thus, insular lobe lesion is observed in 37% of patients with temporal lobe tumor followed by epileptic seizures.

In our study, insular lobe lesion was associated with reduced freedom from surgery after paroxysmal manifestation and increased incidence of seizures compared to isolated temporal lobe neoplasms ($p = 0.017$).
Freedom from surgery after the first seizures depended on histological structure of tumor, its dimensions and type of growth. This period is longer in patients with benign tumors, small neoplasms and intact insula. Conversely, malignant tumors, insular lobe lesion and large neoplasms are associated with earlier surgical treatment.

Insular lobe lesion is followed by bright seizures, as well as combination of two or more types of paroxysms. Paroxysmal disorders caused by insular tumor are characterized by seizures with a motor component, somatosensory paroxysms, autonomic manifestations (respiratory paroxysms, salivation, nausea), speech disorders and taste hallucinations.

Epileptic seizures with vegetative manifestations, as well as olfactory and auditory hallucinations, are characteristic of lesions of both the temporal and insular lobes. Monomorphic seizures with derealization, motor arrest, dysmnesic paroxysms (déjà vu, jamais vu) are more common in patients with temporal lobe lesion compared to the insular lobe. Motor disorders in patients with temporal and insular lobe tumors may be explained by not only fast spread of epileptic activity towards the adjacent opercula and frontal lobe, but also possible localization of epileptic focus within insular lobe per se.

Paroxysms in insular lobe lesion are distinguished by polymorphism. Moreover, paroxysmal structure evolution is followed by faster development of polymorphism compared to isolated temporal lobe lesion. Structural and functional involvement of the insular lobe into epileptic system results early clinical manifestation of disease and earlier surgery in these patients.

The course of disease and treatment strategy in patients temporal and insular lobe lesion depend on histological features, tumor dimensions, severity of insular lobe lesion and structure of paroxysmal disorders. Identification of predictors of insular lesion triggering epileptic seizures makes it possible to suspect insular lobe lesion. The last one is important to determine the prognosis of disease and optimal surgical strategy.

Authors’ participation:
Concept and design of the study — V.Kh., T.A., M.T.
Collection and analysis of data — R.Kh., L.M., T.F., K.S., M.T.
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Anatomy of anterior craniovertebral junction in endoscopic transnasal approach

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Abstract
Modern achievements in endoscopic technologies ensure extending the indications for endoscopic transnasal approach in skull base surgery. Knowledge on topographic anatomy of craniovertebral junction is a prerequisite for surgical interventions in this area. Transnasal endoscopic surgery of craniovertebral junction is a relatively new field. Therefore, this manuscript and similar anatomical studies are extremely important for neurosurgeons.

Keywords: craniovertebral junction, endoscopic transnasal surgery.

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Abbreviations
DM — dura mater
ETA — endoscopic transnasal approach
Craniocervical junction including the occipital bone, Cl and CII vertebrae, ligaments and neurovascular structures is a complex area between the skull and the upper cervical spine. Craniocervical junction ensures stability and movement of the head [1—4]. Congenital malformations, degenerative diseases, injuries, extradural and intradural cancer in this area can result in anterior compression of the upper spinal cord and brain stem [2]. In these cases, anterior approach is a “gold standard” for resection of abnormal structures ensuring direct corridor to inferior segments of clivus and Cl—CII spinal segment without the need for traction of the neurovascular structures [5].

Transoral, transcervical and transnasal approaches are preferred for such interventions [6—8]. Transoral approach is the most common and comprehensively described in the literature. However, recent development of endoscopic technologies is followed by increased interest to endoscopic transnasal access (ETA). In this approach, surgical field is limited by the bone structures (nasal and palatine bones). The last ones form two lines: nasopalatine first proposed by A. Kassam (between the rhinion and posterior edge of the hard palate) and nasocliveal (between the rhinion and lower edge of the clivus). These lines define the triangular shape of surgical approach [9], which ensures an access to the entire ventral part of craniocervical junction in the median plane [10]. Caudal enlargement of this approach is possible through trepanation of posterior segments of hard palate, superior enlargement — using trepanation of inferior part of clivus (Fig. 1). In approach to Cl—CII, surgical field is laterally limited by the Eustachian tubes, medial pterygoid processes, clinoid and supraclinoid segments of internal carotid arteries.

Transnasal approach to dens axis is performed through a small nasopharyngeal incision. Theoretically, this reduces the risk of infectious complications compared to transoral approach due to the lack of the contact with contaminated saliva [11, 12]. Another advantage of transnasal approach compared to transoral access is pathway from top to bottom. This trajectory ensures better control of trepanation of bone structures and visualization of ligaments of dens axis from a more convenient position [13].

The purpose of the study was to analyze the feasibility of endoscopic transnasal approach to the upper cervical spine.

Material and methods

The study was conducted using cadaveric material. There were 15 corpses of adults without lesion of craniocervical junction. Accesses ensuring various angles of surgical manipulations were analyzed. If platybasia and invagination of dens axis were absent, the angle of surgical action in ETA to Cl — CII was 14—16° (median 15±1°). Extended approach through trepanation of inferior segments of clivus and posterior segments of hard palate was followed by augmentation of this angle up to 23—25° (median 24±1°) (Fig. 1).

Certain lesions of craniocervical junction (congenital malformations, basilar impression, platybasia, invagination of dens axis, rheumatoid lesions, etc.) may be accompanied by increased angle of surgical action up to 35° due to abnormally high position of dens axis and additional trepanation of clivus. Indeed, the second point necessary for constructing the nasocliveal line (lower edge of clivus) is displaced up in this case.

Tissue dissection was carried out using various instruments and 0°, 30°, 45° and 70° endoscopes (Fig. 2—7). Vascular filling with colored silicone in accordance with the original author’s technique was applied to visualize arteries and veins [14].

Mean values of surgical angle in ETA were analyzed via assessment of CT scans in 102 patients (44 women and 66 men aged 18—86 years, median 33.9 years) without lesion of craniocervical junction. The angle between the nasopalatine and nasocliveal lines was estimated in sagittal projection. The angle of surgical action in approach to Cl—CII was 8—18° (median 13±5°).

Results

We have worked out all stages of ETA using anatomical specimens.

Dens axis resection was the main stage of approach to the bone and neurovascular structures of craniocervical junction. This measure ensures complete visualization of the underlying subdural structures, anterior brain stem decompression in case of dens axis invagination or other lesion. ETA to craniocervical junction requires a lower trajectory compared to approaches to sella turcica.
An approach to dens axis was started from soft tissue dissection of posterior nasopharyngeal wall in projection of anterior half ring of C1. Monopolar cautery for soft tissue vaporization and scissors are optimal for these manipulations (Fig. 2a–d). Thin prevertebral muscles have a hypovascular zone (white line within the median plane). This area may be used for their lateral retraction or transposition in the form of a U-shaped flap for subsequent closure of the defect [12]. Resection of posterior nasal septum is advisable to extend surgical approach.

Dissection of anterior half-ring of C1 is followed by its trepanation. This procedure was performed by using of a diamond high-speed drill with a diameter of 2—2.5 mm. Cut lines should be carried out vertically with a maximum indentation from the midline within 10—14 mm on each side. This is necessary to prevent damage to the vertebral arteries emerging from the transverse orifices of C1 (foramen transversarium) and lying in the grooves of vertebral artery of C1 (sulcus arteriae vertebralis) (Fig. 3a, b). En-bloc resection of anterior half-ring of C1 is advisable (16—20 mm taking into account thickness of the cut lines) for possible subsequent anterior C0—C1 stabilization in case of its instability [16]. The ligaments between the anterior surface of dens axis and posterior surface of the anterior half-ring of C1 are dissected and vaporized using monopolar cautery.

Anisimova E.A. (2009) reported an important information on the dimensions of bone structures of C1—CII spine segment. The author analyzed 70 bone anatomical specimens of C1—CII spine segment: C1 anterior arch height is 7—17 mm (median 11 mm), C1 anterior arch width — 13—22 mm (median 19 mm), height of CII body with a dens axis — 29—44 mm (median 39 mm), height of CII body without a dens axis — 15—26 mm (median 23 mm), height of C1 and CII in anatomical position — 15—26 mm (median 23 mm) [17]. These data are valuable for anterior trepanation of C1—CII spine segment.

The upper part of the dens axis may be covered by inferior segments of clivus in case of high position of dens axis. Thus, trepanation of these parts of clivus is required to achieve the highest parts of dens axis.

Next, dens axis and upper parts of CII body were skeletonized. After that, the neck of dens axis is intersected as close as possible to the CII body (Fig. 4a—d). The next stages are stepwise trepanation of dens axis,
its drilling from the inside up to the cortical plate of posterior surface. The last one is thinned and then may be fragmented by using of Kerrison nippers or dissected as a single block from the underlying dura mater. Resection of the invaginated dens axis should be done delicately considering thinning of the underlying DM. Indeed, DM perforation will result cerebrospinal fluid leakage and require plastic closure of the defect.

Dens axis is fixed by a complex ligamentous system (pterygoid, apical and cruciate ligaments). Pterygoid ligaments are composed of thin fibrous tissue and connect the dens with occipital condyles. Apical ligament is localized in the midline and connects dens axis with the edge of foramen magnum in the occipital bone. All these ligaments should be intersected to resect dens axis.

DM is opened by using of scissors if examination of subdural space is required (surgery for intradural tumors) (Fig. 5). DM dissection is followed by visualization of the underlying neurovascular structures (Fig. 6).

We report an example of application of the developed surgical technique.

**Case report**

A 22-year-old patient S. was hospitalized to the Burdenko Neurosurgery Center on June 18, 2018. Platybasia and dens axis invagination followed by compression of medulla oblongata were diagnosed (Fig. 7a–d). Occipitospondylodesis has been previously carried out at the Priorov Center for Traumatology and Orthopedics on March, 2018 (Fig. 7b). Clinical signs were periodic breathing impairment, numbness of the fingers and severe headache. Endoscopic transnasal resection of the invaginated dens axis and brainstem decompression were performed on June 20, 2018. Total resection of the invaginated dens axis and brainstem decompression were intraoperatively achieved.

Mild postoperative transient bulbar disorders were noted. The patient was discharged in 12 days after surgery. Above-mentioned preoperative symptoms completely regressed within 6 months after surgery.

**Discussion**

Knowledge on the topographic anatomy of craniovertebral junction is a prerequisite for surgery in
this area. Close localization of critical structures (brainstem, major vessels) causes an extremely high risk of surgeries for various lesions of craniovertebral region.

Endoscopic transnasal surgery of craniovertebral junction is a relatively new direction. Therefore, the question of possible intraoperative features and postoperative complications remains relevant.

Bleeding is the main intraoperative complication. In this regard, hemostasis is one of the potential problems associated with endonasal approach. Modern hemostatic agents and instruments designed for endoscopic endonasal surgery including diamond drills and bipolar cautery ensure safe procedures [18].

Intraoperative CSF leakage is an important problem. In case of resection of extradural structures, intraoperative CSF leakage develops after DM injury. Probably, this is associated with limitations of two-dimensional vision that is typical for endoscopic technologies in contrast to 3D imaging ensured by microscope during transoral surgery [19]. According to the modern data, incidence of intra- and postoperative CSF leakage in transnasal endoscopic surgery for CVJ lesion is approximately 12%. However, the use of modern antibiotics can reduce the incidence of meningitis up to 1—2% [19, 20].

Repair of a bone-dural defect within craniovertebral junction and clivus is a difficult problem in endoscopic transnasal surgery. This is due to not only defect dimensions, but also active CSF flow and the absence of supporting structures necessary for fixation of plastic material [21]. Combination of free transplantation methods (fatty tissue and fascia) and pedicled flaps is preferred for closure of the bone-dural defect in this area. The “triple F” technique (fat, fascia, flap) is mainly used [18, 22].

Other possible postoperative complications are transient pharyngeal insufficiency (swallowing and speech impairment, 6% of patients), epistaxis (up to 2%) and impaired breathing up to the need for tracheostomy (up to 2%) [19, 20, 23].

It should be noted that endoscopic transnasal approach to craniovertebral junction is associated
with increased surgery time and longer learning curve compared to other techniques [24–28].

**Conclusion**

The proposed technology for endoscopic transnasal approach ensures extended possibilities in surgery of craniovertebral junction and favorable postoperative outcomes along with transoral microsurgical technique. In some cases, endoscopic transnasal surgery may be the only option for surgical treatment.

**Authors’ participation:**
- Concept and design of the study — A.Sh., V.N., I.Ch.
- Collection and analysis of data — A.Sh., I.Ch., D.A., M.Sh., K.Ch.
- Writing the text — A.Sh., I.Ch.
- Editing — A.Sh., V.N.

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**Fig. 7. Pre- and postoperative MR and CT scans in the patient S.**

a — preoperative MR scans (T2 and T1WI). Platybasia, dens axis invagination followed by compression of medulla oblongata. Red dashed line — nasopalatine line, yellow dashed line — nasoclival line, yellow arch — angle between the nasopalatine and nasoclival lines (35°). b — preoperative CT and x-ray scans. Occipitospondylodesis is performed; c — postoperative CT scans, axial and sagittal planes. Complete brain stem decompression. Red dashed line — nasopalatine line, yellow dashed line — nasoclival line, red arch — angle between the nasopalatine and nasoclival lines (35°). Trepanation of the lower segments of clivus is additionally performed to achieve the upper parts of dens axis; d — T2WI and T1WI in 9 days after surgery.
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The manuscript is devoted to a complex part of neurosurgery. Transnasal endoscopic surgery of craniovertebral junction is a relatively new direction in the world. Only few reports devoted to this issue are published in the literature. In this regard, similar anatomical studies are extremely important and promising for neurosurgeons and further development of this method. Complex surgical topography and anatomy, especially in patients with congenital and acquired deformities and neoplasms, necessitate the use of new techniques for their analysis.

The authors comprehensively studied cadaveric material and developed certain postulates and features of this endoscopic approach. Description of various details depending on anatomical features is extremely valuable. Conclusions are supported by CT data. Results are illustrated by a qualitative clinical example. The proposed technology allows you to expand surgical capabilities in this complex area and ensure favorable postoperative outcomes. The manuscript meets all the requirements of modern scientific analysis and will decorate any neurosurgical journal.

V.Yu. Cherebillo (St. Petersburg, Russia)
Spinal cord metastasis of anaplastic oligodendroglioma of the brain without recurrence of primary tumor. Case report and literature review

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Abstract

Spinal cord metastases of brain gliomas are rare. However, incidence of these tumors has been increasing recently. The vast majority of neurosurgeons and oncologists recognize spinal cord metastasis of malignant brain glioma followed by symptoms of transverse spinal cord lesion as non-curable terminal stage of malignant process. In this paper, we report a rare clinical case of metastatic spinal cord lesion in a patient after previous surgery for anaplastic oligodendroglioma of the right frontal lobe. There were no signs of local recurrence of the primary tumor. Active surgical strategy followed by radio- and chemotherapy significantly improved the patient’s quality of life. Postoperative follow-up is 6 months by the moment of writing the manuscript, no clinical signs of progression are observed.

Keywords: glioma, oligodendroglioma, metastasis.

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Spinal cord metastases of brain glioma are rare. However, incidence of these tumors has been increasing over the last time. The causes are prolonged life expectancy in patients with brain gliomas on the background of modern complex therapy and improved diagnosis. The last one is associated with a widespread clinical introduction of magnetic resonance imaging (MRI) with a high magnetic field strength. The absolute majority of neurosurgeons and oncologists recognize spinal cord metastases with symptoms of transverse spinal cord lesion as an incurable terminal situation in a patient with malignant brain glioma. Indeed, it is currently impossible to predict the life expectancy in similar patient, especially in case of metastatic process following progression of the primary tumor.

Most physicians refuse to continue active treatment in these patients. Such pessimism is not always justified. We report a rare clinical case of metastatic spinal cord lesion in a patient who had previously undergone surgery for anaplastic oligodendroglioma of the right frontal lobe. There were no signs of local tumor recurrence by the moment of spinal disorders. Active surgical approach for metastatic spinal cord tumor followed by radio- and chemotherapy significantly improved patient’s quality of life. No clinical signs of tumor progression were noted within 6 months after surgery.

Clinical case

A 60-year-old patient M. was hospitalized to the neurosurgical department of the Kozhevnikov Clinic of Nervous Diseases (Sechenov First Moscow State Medical University) in March 2019. Upon admission, she complained of severe weakness in the legs and hands, cervical spine pain with irradiation to the hands, no sensitivity disorders was observed after surgery. The wound healed via primary intention.

The first symptoms occurred at the end of September 2018 with subsequent gradual deterioration. By the beginning of January 2019, the patient could walk only with support. Movements have become impossible since March 2019.

Contrast-enhanced MRI of the cervical spine was performed on February 16, 2019. Dorsal tumor of the spinal canal with unclear irregular contours and heterogeneous solid structure (hyperintense in T2 mode and hypoointense in T1 mode) was diagnosed. The tumor $2 \times 1.1 \times 3.3$ cm was localized at the level of CVI—ThI. Focal lesion was accompanied by severe widespread edema of the spinal cord. Intravenous contrast enhancement was followed by intense heterogeneous amplification of MR signal from the tumor, heterogeneous widespread accumulation of the contrast agent by the meninges of the spinal cord and pia mater covering ventral surface of the medulla oblongata (Fig. 1).

Cystic solid mediobasal tumor of the right frontal lobe spreading under cerebral falx was previously found in March 2014 (Fig. 2). Osteoplastic right-sided fronto-temporal craniotomy, total resection of cystic solid intracerebral tumor of the right frontal lobe were carried out at the Petrovsky Russian Research Center of Surgery on May 25, 2014. Histological examination confirmed anaplastic oligodendroglioma (WHO Grade III). Surgery was followed by radiotherapy with a total focal dose of 60 Gy (30 fractions). Symptoms of metastatic spinal cord lesion occurred in 4 years and 4 months after resection of brain glioma.

No data on primary tumor recurrence were obtained at admission for spinal metastasis (Fig. 3).

Upon admission to the neurosurgical department of the Clinic of Nervous Diseases, symmetric high tendon reflexes from both legs, plantar hyperesthesia, mosaic impairment of pain and temperature sensitivity below inguinal folds, distal paresis of the right arm up to 3 points were observed. There was paresis of lower limbs up to 1—2 points and axial muscles. The patient could not move, sat only with support, and needed permanent outside care (McCormick grade IV).

CVI—CVII laminectomy, TI upper arctomy, resection of extra-intramedullary spinal cord tumor at the level of CVI—TI were carried out on March 28, 2019.

The tumor loosely fused with the inner surface of dura mater that required surgical dissection. The neoplasm was localized on the surface of the spinal cord and spread inside. Pia mater of the spinal cord was opaque and had a red color above and below the tumor (Fig. 4). Total resection of tumor was performed.

Postoperative period was uneventful. Reduced area of sensitive disorders was observed after surgery. The wound healed via primary intention.

Histological examination revealed rounded cells with round nuclei, optically empty cytoplasm in some cells, few mitoses and vessels with advanced endothelial pro-

Fig. 1. MRI of cervical and upper thoracic spine.

Widespread leptomeningeal spinal cord lesion with a solid dorsal node at the level of CVI—ThI. a — T2, sagittal plane. Widespread spinal cord edema throughout the studied area. Dorsal extramedullary tumor is visible at the level of CVI—ThI. Hyperintense MR-signal from the tumor is poorly differentiated with a signal from edematous spinal cord; b — T1, sagittal plane. Tumor node is isoointense to brain tissue and not differentiated during native survey; c — T1 with contrast enhancement, sagittal plane. Intensive accumulation of contrast agent by the tumor node and widespread leptomeningeal lesion. Dorsal surface of the spinal cord is predominantly affected. There is a thin area of leptomeningeal lesion of the medulla oblongata.
Clinical practice

Liferation and focal necrosis. Immunohistochemical examination showed positive expression of glial fibrillary acidic protein, synaptophysin, vimentin, NSE, negative EMA expression, CD34 expression in vascular walls. Ki-67 index was 25%. Genetic survey revealed 1p/19q co-deletion (Fig. 5). Histological diagnosis was anaplastic oligodendroglioma with 1p/19q co-deletion.

Considering mild relief of sensitive disorders, McCormick grade was the same at discharge (IV). Neurological disorders and lower limb weakness gradually regressed. The patient began to get up and walk with support. Radiotherapy has been performed for the period from 20.05.2019 to 24.06.2019 (total focal dose 36 Gy, single focal dose 2 Gy). At the time of writing this manuscript (6 months after surgery), a standard course of chemotherapy with temozolomide was being carried out. The patient takes care of herself and does not need for constant outside care (McCormick grade III).

Discussion

Metastases is a rare but well-described complication of brain glioma. Two terms are used to describe these metastatic tumors: extra-neural metastases (outside the central nervous system) and extra-cranial metastases (metastatic lesion of spinal cord matter and sheaths) [1]. Recently, incidence of extracranial metastases of glial tumors is being increased. This is explained by improved quality of diagnosis and widespread introduction of MRI (including spine and spinal cord) in postoperative period throughout radiotherapy, chemotherapy and later. The second cause is increased life span in patients with gliomas following modern schemes of complex treatment [2, 3].

According to modern data, incidence of extraneural metastases in patients with malignant brain gliomas is 2%. Metastases are diagnosed in 2 years after detection of the primary tumor. In the vast majority of cases, metastatic lesion occurs after surgery for brain tumors or ventriculoperitoneal bypass [4].

Rare extraneural and extracranial metastases without previous resection of glioma are associated with the absence of lymphatic system in the central nervous system, no communication between brain subarachnoid space and lymphatic system, weak communication of intracerebral perivascular spaces with skull subarachnoid space and thin cerebral veins which are thrombosed under pressure before tumor spread into their lumen [5, 6].

Increased risk of metastases of glioma after neurosurgery is explained as follows. The risk of hematogenous spread of tumor cells is increased due to possible migration of microscopic fragments through the transected

Fig. 2. MRI of the brain before the first surgery in 2014.

Intracerebral cystic medio-basal tumor of the right frontal lobe with invasion under the falk and severe compression of the left frontal lobe. Solid node is located medi ally, dislocated under the falk and partially located on the left. a — T2, axial plane. Hyperintense signal of cystic fluid is similar to CSF. Slightly hyperintense signal of solid tumor node is different from the brain matter; b — T1, axial plane. Hypointense signal of cystic fluid is similar to CSF. Slightly hypointense signal of solid tumor node differs from that of brain matter; d — T2, frontal plane, dislocation of a solid node under the falk is clearly visible. Contrast-enhanced MRI: c — axial plane, e — frontal plane, f — sagittal plane. Heterogeneous accumulation of contrast agent inside the solid node.
outflow veins. Moreover, risk of intraoperative dissemination of tumor tissue through cerebrospinal fluid is also increased due to dissection of subarachnoid space and ventricular walls [7].

Hematogenous extraneural metastases are very typical for glioblastoma. Oligodendroglioma extremely rarely metastasizes through hematogenous pathways into extraneural structures. G. Li et al. (2014) reviewed 61 patients with metastases of oligodendroglioma. Bone and lymph node metastases were the most common. In single cases, metastases to lungs, pleura, soft tissues and abdominal organs were described [8].

Metastases to the spinal canal through cerebrospinal fluid is common for medulloblastoma. However, this tumor belongs to the histological group of embryonic neoplasms and is not included into the group of diffuse astrocytic and oligodendroglial tumors. The last ones are currently determined as "gliomas" in narrow interpretation [9]. Malignant astrocytic glia and oligodendroglioma are the second neoplasms with common metastasizing through cerebrospinal fluid after medulloblastoma [10].

Multiple metastatic lesions of spinal cord sheaths without large metastatic nodes (similar to carcinomatosis) have been described in patients with malignant gliomas since the last century. Incidence of these lesions is up to 20% in patients with glioblastoma and anaplastic astrocytoma, 8.5—14% in anaplastic oligodendroglioma [11, 12]. Nevertheless, large metastases followed by lesion of the spinal cord and spinal roots are rare.

In 1926, P. Bailey and H. Cushing first described spinal metastases in patients with brain glioma [13]. Pathogenesis of metastatic lesion of the spinal cord may be different in patients with brain gliomas. The most obvious pathways are migration of microscopic fragments of tumor tissue through cerebrospinal fluid with subsequent penetration into spinal cord matter through the perivascular Virchow-Robin spaces and migration through the open central canal. The second mechanism may be fixation of tumor cells on pia mater and subsequent growth
of metastatic node into the spinal cord [14, 15]. Hematogenous dissemination of tumor fragments directly into spinal cord matter is also possible, although this mechanism seems unlikely to us.

In 2011, C. Kural et al. described a rare case of temporal lobe anaplastic oligodendroglioma with multiple metastatic spinal lesion diagnosed in 11 months after brain surgery. There was severe extradural compression of the spinal cord at the level of ThIV caused by tissue component of the epidural tumor. The authors supposed that multiple metastatic spinal cord lesion is associated tumor cell dissemination through the brain veins during surgery for primary tumor and their penetration through the sinuses into epidural venous plexus of the spine [16].

Currently, 18 patients with metastatic spinal cord lesion following brain oligodendroglioma are described in the literature including our observation. A. Elefante et al. (2012) analyzed their own clinical observation and 16 cases found in the literature [15]. Age of patients varied from 6 to 73 years (mean 37 years). The interval between brain tumor resection and diagnosis of spinal lesion ranged from 3 months to 7 years (mean 25.5 months). In case of anaplastic oligodendroglioma (Grade III), metastatic lesion occurs in 21 months after surgery, in oligodendroglioma (Grade II) — after 30 months. Damage to spine sheaths with local tumor spreading into the spinal cord was noted in 14 cases, isolated intramedullary tumor — in 3 cases.

In 2006, R. Merrell et al. suggested that metastasizing through cerebrospinal fluid pathways in patients with oligodendroglioma is more typical for tumors with 1p/19q deletion [17]. In our opinion, this conclusion is controversial, since the higher risk of metastasizing is probably associated with better effect of radio- and chemotherapy in these patients and increased life expectancy rather genetic abnormality per se.

Simultaneous diagnosis of brain oligodendroglioma and metastatic spinal cord lesion is rarely described in the literature. M. Natale et al. reported metastatic lesion of spinal roots (cauda equina) preceding severe symptoms of anaplastic brain oligodendroglioma [18].

In our case, metastatic spinal cord lesion was not accompanied by local recurrence of intracranial tumor. Only Ozişik PA et al. described a similar patient in 2008 [19].

It should be noted that the number of patients with metastatic spinal cord lesion is quite comparable with the number of descriptions of primary spinal oligodendroglioma. In 2005, K.N. Fountas et al. analyzed several large surgical series and case reports and found only 50 cases of primary spinal oligodendroglioma. Children comprised a significant number of these patients. Anaplastic oligodendroglioma (Grade III) was detected in 12% of cases.

Over the past 10 years (2009—2018), 848 adults underwent surgical treatment for intramedullary tumors at the Burdenko Neurosurgery Center and Sechenov First Moscow State Medical University. Primary oligodendroglioma was detected in only one case.

Considering these data, obvious success in complex treatment of brain oligodendroglioma and further increase in the life expectancy of these patients, augmentation of the incidence of metastatic spinal cord lesion may be supposed in patients with brain oligodendroglioma. The problem of optimal treatment strategy in these patients should be considered in more detail.
**Conclusion**

Despite small incidence of brain glioma metastases to the spinal canal and spinal cord, back pain and other symptoms associated with spinal cord lesion in patients with previous glial brain tumors is an indication for magnetic resonance imaging of the spine and spinal cord to identify possible metastases. Metastatic spinal cord lesion can occur in the absence of clinical and neuroimaging signs of primary tumor.

Treatment of metastatic spinal cord lesion in patients with brain glioma is not standardized. Indications for surgical treatment are unclear. In our opinion, solitary spinal cord tumor without obvious signs of extensive leptomeningeal lesion can be resected. In case of leptomeningeal metastasis combined with nodular lesion of the spinal cord, indications for surgery are determined by the need for biopsy, spinal cord decompression, and analysis of appropriateness of radiotherapy.

This case report shows that even a patient with severe neurological deficit and widespread leptomeningeal lesion has a chance of improvement after spinal cord decompression and subsequent radio- and chemotherapy.

**Authors’ participation:**
Concept and design of the study — G.E., N.K.
Collection and analysis of data — G.E., S.V.
Writing the text — V.A.
Editing — G.E., S.V., N.K., S.T.

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REFERENCES


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Glioblastoma in the region of previously resected meningioma. Case report and literature review

© V.V. Nazarov1, N.N. Linde2, D.S. Kim1, G.V. Danilov1, V.A. Cherekaev1, A.V. Kozlov1

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Abstract
Combination of meningioma and glioblastoma within the same anatomical region is casuistry. We found only 13 case reports in the available literature. Some of the authors reported induced nature of the second tumor, i.e. development under the influence of the primary neoplasm. We report a patient with glioblastoma of the right frontoparietotemporal region in 3 years after previous resection of benign right-sided meningioma of sphenoid wings. Mathematical analysis of the discovered pattern resulted conclusion about its random nature, i.e. no causal relationship between both neoplasms.

Keywords: meningioma, glioblastoma, one patient.

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Abbreviations
IHS — immunohistochemical study
CT — computed tomography
MRI — magnetic resonance imaging
PCR — polymerase chain reaction
DM — dura mater
CNS — central nervous system
Meningioma and glioblastoma are characterized by significant histological and molecular-biological differences and determined as different diseases [1]. Risk factors of these tumors are also different. The likelihood of meningioma is increased after irradiation [2] while the risk of glioblastoma is influenced (2-fold decrease) only by the presence of allergic diseases [3]. The third and last known factor is relatives with brain tumor. This aspect equally (about 2 times) increases the risk of both tumors [4, 5].

Meningioma and glioma in the same patient were first described by H. Cushing in 1938 [6]. A.J. Strong first reported both tumors in the same anatomical region in 1976 [7]. Analysis of the Pubmed database using the keywords “meningioma”, “glioblastoma”, “simultaneous”, “same patient” revealed 60 case reports published by March 31, 2020. More comprehensive analysis revealed that various authors designated a tumor of other histological structure or malignancy grade as “glioblastoma” in 15 manuscripts. It should be noted that the unified criteria for CNS tumor classification were formulated only in 1979 and then repeatedly revised. Histological classification of meningiomas and glioblastomas has remained the same since 1993. Thus, 45 more or less reliable descriptions of meningioma combined with glioblastoma in the same patient are currently presented in the available literature. In 14 manuscripts (taking into account this report), both tumors in the same anatomical region are described (Table) [7—18]. Despite the rarity of these observations, some authors describe the possible pathogenetic mechanisms of the development of glioblastoma under the influence of meningioma or surgical trauma. At the same time, other researchers deny a causal relationship in this situation. In our opinion, it is appropriate to report our own observation and assess the likelihood of a causal relationship between the occurrence of both neoplasms in the same anatomical region.

Case report

A 69-year-old patient N. was hospitalized to the Burdenko Neurosurgery Center on March 19, 2015. The complaints were severe headache with aggravation in the morning, nausea and vomiting associated headache, dizziness, general weakness and inability to walk without assistance. Headache and dizziness appeared about 1 year ago. MRI of the head was performed but diagnostic data were lost. Neurosurgeon recommended follow-up. Subsequently, headache and dizziness intensified. Staggering forward and lurch occurred. Inability to walk without assistance and weakness in the left limbs were noted from the beginning of 2015. Repeated MRI on February 2015 revealed multiple focal lesions associated with dura matter in the region of the tubercle of sella turcica, sphenoid bone, medial parts of sphenoid wings on the right, left parietal region, left occipitoparietal area over the cerebellum. The largest tumor node (3.9×5×4.9 cm) was localized within the outer parts of sphenoid wings on the right. This node was accompanied by peripheral contrast enhancement of DM, severe perifocal edema and left-sided brain dislocation by 8 mm (Fig. 1a). Upon admission, general cerebral symptoms (headache with nausea and vomiting in case of deterioration, impaired memory) were associated with astasia-abasia (inability to stand and walk in a normal manner without coordination impairment), left-sided hemiparesis up to 4 scores, right-sided hemi-paresis. Karnovsky score [19] at admission was 50 points. Treatment with intramuscular injections of dexamethasone 12 mg on the first day and 8 mg in the next days improved this score up to 60 points.

Microsurgical resection of right-sided meningioma of the outer parts of sphenoid wings was performed on March 24, 2015. Surgery was carried out without any features. Macroscopically total resection was combined with excision of dura mater within the matrix area (followed by defect closure with a periosteal graft) and bone (followed by repair with polymethylmethacrylate). Resection quality was determined as Simpson type 1 [20]. The tumor was in a thin arachnoid capsule. Local adhesions with a pial membrane without cortical invasion were observed. Postoperative period was uneventful. Control CT (Fig. 1b) did not reveal tumor remnants or postoperative complications on the background of persistent perifocal edema and median dislocation by 5 mm.

In neurological status, regression of left-sided hemiparesis and astasia-abasia was noted. The patient walked without assistance, took care of herself. Headache, nausea and vomiting disappeared and memory improved. Karnovsky score at discharge (the 7th day after surgery) was 90 points.

Histological examination of specimen revealed the fragments of tumor tissue with a heterogeneous structure. One part of the tumor was represented by the cells with eosinophilic cytoplasm and round vesicle-like nucleus. These cells formed solid fields and micro-concentric structures. Other part consisted of elongated cells with oval nuclei, which formed bundle structures. Foci of severe fibrosis and angiomatosis with initial signs of vascular endothelial proliferation were observed in the tumor stroma. Moreover, single mitoses and foci of intraoperative hemorrhages were also visualized in the tumor stroma.

Immunohistochemical analysis of tumor cells revealed positive nuclear expression of progesterone (PR), positive membrane expression of epithelial membrane antigen (EMA) and positive stromal expression of Vimentin in complete absence of glial fibrillar acidic protein (GFAP) in tumor tissue. Proliferative index Ki-67 was 4—5% in some foci.

Thus, the morphological features and immune phenotype of tumor corresponded to meningioma with a mixed structure, stromal fibrosis and single mitoses (WHO Grade I, ICD-O3-9537/0) (Fig. 2).

Contrast-enhanced MRI in 3 months after surgery and then annually was recommended. This recommen-
### Literature data on combination of meningioma and glioblastoma in the same patient

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<td>Right fronto-parietal</td>
<td>Right frontal</td>
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<td>Left frontal</td>
<td>Left frontal</td>
<td>Right temporal</td>
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<td>Left frontal</td>
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<td>Light microscopy</td>
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<td>ICS GFAP+</td>
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<td>ICS, PCR IDH1wt</td>
<td>ICS GFAP+, EMA+</td>
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<td>Radiotherapy</td>
<td>Radiotherapy + chemo-therapy according to Stupp protocol</td>
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<td>Unknown</td>
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<td>Unknown</td>
<td>14 months</td>
<td>Over 6 months</td>
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*Note. * — after the diagnosis of glioma. ICS — immunohistochemical study; PCR — polymerase chain reaction; GFAP — glial fibrillar acidic protein; EMA — epithelial membrane antigen.
Transient headache, dizziness and lurch have occurred since summer in 2018. On her own initiative, the patient performed contrast-enhanced MRI of the brain in October 16, 2018 (Fig. 1c). There was no obvious progression of any of the previously observed primary multiple meningiomas. However, multinodular tumor in the right fronto-parieto-temporal region with annular contrast enhancement and mild mass-effect was found.

The patient was hospitalized to the Burdenko Neurosurgery Center on October 29, 2018. Neurological examination revealed moderate general cerebral symptoms (headache), mild central paresis of the left facial nerve, predominance of deep reflexes from the left limbs, left-sided Babinski sign, impaired balance in Romberg’s test, no coordination impairment. Karnofsky score was 70 points. Microsurgical resection of the tumor of the right fronto-parieto-temporal region was performed on October 31, 2018. Gray-yellow tumor was characterized by

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**Fig. 1. Survey data in the patient N.**

a — contrast-enhanced MR scans (25.02.2015); b — postoperative contrast-enhanced CT scans (24.03.2015); c — contrast-enhanced MR scans in 3 years after resection of benign meningioma (16.10.2018).
focal decay, hemorrhages and black thrombosed vessels. Tumor stroma was localized in the brain matter, had no clear boundary with white matter and did not attach to the dura mater. Obvious tumor tissue was resected within the visible boundaries. Control CT did not reveal any tumor remnants or surgical complications. Perifocal zone was not excised and aggravation of weakness in the left leg up to 3 scores was observed in postoperative period. Nevertheless, paresis regressed up to 4 points, headaches and dizziness disappeared and Karnofsky score increased up to 70 points by the moment of discharge in 8 days after surgery.

Surgical specimen was represented by small fragments of gray-pink tissue with a yellow tint and heterogeneous density. Microscopic examination revealed the fragments of malignant glial tumor tissue with diffuse growth. A tumor with high cell density was represented by polymorphic astrocytes with round, oval and irregular nuclei, and uneven chromatin distribution. There were cells with hyperchromic basophilic nuclei, as well as multiple atypical mitoses (up to 13 in 1 field of view under 400-fold magnification). Massive proliferation of vascular endothelial cells was detected in the tumor tissue. Large areas of necrotic changes with shadows of cells and vessels, apoptotic bodies, as well as multiple foci of necrosis with pseudo-palisade structures were observed in the tumor stroma. There were the foci of previous hemorrhages with intracellular accumulation of a brown pigment (hemoglobin) and areas of fresh hemorrhages.

IHS revealed positive expression of GFAP, Vimentin, positive membrane expression of EMA in certain foci of tumor cell clusters, and no nuclear expression of PR. Proliferative index was 25—30%. Molecular genetic examination (real-time PCR and Sanger sequencing) did not reveal a mutation in the codon 132 of the IDH1 gene (isocitrate dehydrogenase) and in the codon 172 of the IDH2 gene. Molecular genetic testing (real-time PCR) did not reveal a V600E mutation (replacement of valine with glutamic acid at the position 600) in the BRAF gene. Methyl-specific signal was also not detected that indicates the absence of MGMT gene promoter methylation (O6-methylguanine DNA methyltransferase). EGFR gene amplification (epidermal growth factor tyrosine kinase receptor) was detected by using of in situ fluorescence hybridization.

Considering molecular genetic data, the morphological picture and immune phenotype of the tumor corresponded to glioblastoma IDH-wild type, WHO Grade IV, ICD-O3-9440/3. The absence of a V600E mutation in the BRAF gene made it possible to exclude the epithelioid variant of glioblastoma (Fig. 3).

Considering the histological diagnosis, postoperative chemo- and radiotherapy was recommended in standard fashion (gamma therapy with fractions of 1.8 Gy per a focus with 1—1.5 cm marginal covering for 5 days a week up to a total focal dose of 60 Gy, daily intake of temozolomide 70 mg/m²). Then, chemotherapy alone with temozolomide 200 mg/m2 daily was prescribed for 5 days (interruption of 21 days, a total number of courses – 6). Ac-
According to phone interviewing in 6 months after surgery, the patient felt satisfactory and took care for herself. Contrast-enhanced MRI of the head was recommended. The further fate of the patient is unknown.

**Discussion**

To date, 13 cases of meningioma and glioblastoma in the same anatomical region have been described in available literature (Table). Our case report is the 14th description. Importantly, the diagnosis of both tumors in our case was confirmed by light microscopy, IHS and PCR. Considering the development of both tumors in the same area, various researchers supposed a single mechanism of their oncogenesis.

We know only one hereditary disease predisposing to the development of meningioma and glioblastoma. It is Li-Fraumeni syndrome. This syndrome is based on TP53 gene lesion (a transcription factor regulating the cell cycle of the p53 protein). P53 protein is involved into cellular signaling pathways common for meningioma and glioblastoma. However, soft or bone tissue sarcoma under the age of 46 years and two relatives with a cancer or sarcoma diagnosed under the age of 46 years are required for the diagnosis of this syndrome [20]. Moreover, this syndrome is associated with breast cancer in 90% of women by the age of 60 years. Li-Fraumeni syndrome may be excluded in our case considering the absence of these diseases.

A hypothesis about possible induction of oncogenesis of meningioma by the cells of previous malignant tumor was suggested [17]. However, the authors have not described a specific mechanism, and the sequence of tumors was reversed in our case.

For a long time, there was an opinion about traumatic brain injury as an etiological factor of brain tumors. H. Cushing kept up this theory too [6]. Considering this concept, K. Zülch suggested that brain trauma during meningioma resection can result a gliosis zone with subsequent transformation into glioma (including glioblastoma) [21]. However, injury is currently not mentioned among the risk factors of brain tumors [22], and, with all respect to the authority of K. Zülch, we cannot agree with this opinion.

There is an opinion about the occurrence of irradiation-induced glioma (and glioblastoma) after radiotherapy for inoperable meningioma. In our case, irradiation after total (Simpson type 1) resection of benign meningioma was not carried out and was not even considered.

We failed to find other hypotheses on the occurrence of meningioma and glioblastoma in the same anatomical region.

At the same time, elementary mathematical analysis indicates the absence of a relationship between these events. Thus, we talk about the random match of tumors. It is possible to approximately estimate the probability of simultaneous diagnosis of meningioma and glioblastoma in one patient within a year using the methods of classical probability theory. Incidences of both tumors are used for these calculations.

Annual incidence of meningioma is 8.56 per 100,000, glioblastoma — 3.22 per 100,000 [1]. A theoretical prob-

Рис. 3. Глиобластома: микрофотографии гистологических препаратов, полученных после операции пациентки Н. от 31.10.18.

а — окраска гематоксилином и эозином, ×100; б — окраска гематоксилином и эозином ув. 200; в — позитивная экспрессия GFAP (Glial fibrillary acidic protein); г — индекс метки (ИМ) Ki-67, ×200.
Clinical practice

ability (using the product of probabilities) of the occurrence of meningioma and glioblastoma in the same patient is approximately equal to $2.5 \times 10^{-9}$ throughout one year. Mean population is 6.5 billion people over the past 30 years. Thus, a similar combination of tumors could be annually detected in approximately 16 patients in the world. In other words, it is theoretically possible to identify about 50 cases of brain glioma and meningioma for a 3-year follow-up. The probability of the development of meningioma in one anatomical zone will be approximately $10^{-5}$, glioblastoma — $4 \times 10^{-6}$, if appearance of each tumor in one of eight anatomical regions (frontal, parietal, temporal, and occipital on each side) is considered equally probable. Annual probability of detecting two tumors (according to the product of probabilities) is approximately $4 \times 10^{-11}$. Thus, we can expect 1 patient with meningioma and glioma in the same anatomical area throughout 5 years. Therefore, this combination is very rare. Obviously, simultaneous detection of meningioma and glioblastoma within several years determines higher incidence of this event. Thus, considering a world population approaching 8 billion, such cases can occur every 1—2 years. There are only 14 case reports in available literature taking into account our observation. We see that the number of published reports on meningioma and glioblastoma in one anatomical region is lower in comparison with the calculated probability of an accidental coincidence of both diseases.

**Conclusion**

In our opinion, the low probability of occurrence of meningioma and glioblastoma in one patient does not exclude an accidental combination of these diseases. Thus, we cannot talk about certain general mechanisms of oncogenesis of meningioma and glioblastoma.

**Authors’ participation:**
Concept and design of the study — A.K.
Collection and analysis of data — V.N., N.L., D.K., V.Ch., A.K.
Statistical analysis — G.D., A.K.
Writing the text — V.N., N.L., V.Ch., A.K.
Editing — V.Ch.
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Microsurgical resection of multiple unruptured cerebral AVMs. Case report and literature review

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Abstract
Multiple brain arteriovenous malformations (AVMs) are extremely rare. We report a 26-year-old patient with paroxysmal symptoms. This was the first case in our center over 10 years (0.15% of all patients with brain AVM in this period). Microsurgical resection of AVM of the left temporal lobe was carried out at the first stage (Spetzler—Martin grade I). A month later, resection of AVM of the left parietal lobe (Spetzler—Martin grade III) after preliminary endovascular embolization was carried out. Early postoperative visual and mental disorders occurred after the second surgery and completely regressed within 1 month. Control angiography after the second operation confirmed total resection of both AVMs. Thus, staged microsurgical resection of two cerebral AVMs combined with preliminary endovascular embolization of more complex AVM was effective and ensured favorable clinical result. We analyzed the features of our clinical case and compared our findings with literature data.

Keywords: arteriovenous malformations, unruptured AVM, multiple AVMs, microsurgical treatment of AVM.

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Abbreviations
AVM — arteriovenous malformation
ICH — intracranial hypertension
PCA — posterior cerebral artery
MRI — magnetic resonance imaging
OWRD — Osler-Weber-Rendu disease
MCA — middle cerebral artery
CAG — cerebral angiography
Arteriovenous malformation (AVM) of the brain is a rather rare vascular disease. Annual incidence of this lesion is 1.1—1.4 per 100,000 [1—3]. Multiple AVMs are observed only in 0.3—4% of patients with this disease [4—9]. Children or young adults are more common to be diagnosed with AVM [5, 7]. There is no generally accepted treatment algorithm of these patients due to rarity of this disease.

We report a patient who underwent stage-by-stage microsurgical resection of two AVMs of the brain.

Case report

A 26-year-old man appealed for a medical care about a generalized convulsive epileptic seizure arose in one's sleep. Neurologist recommended an examination.

Magnetic resonance imaging (MRI) of the brain revealed two AVMs in different brain lobes (within the pole of the left temporal lobe and medial parts of the left parietal lobe). There were no MR signs of hemorrhage from any AVM (Fig. 1).

According to cerebral angiography (CAG) data, blood supply of AVM in the left temporal lobe was achieved through the left middle cerebral artery (MCA), venous outflow – into the left transverse sinus (Fig. 2). Blood supply of AVM in the left parietal lobe was achieved through the left MCA and posterior cerebral artery (PCA) (originating from internal carotid artery), venous outflow – into superior sagittal sinus (Fig. 2).

According to Spetzler – Martin grading system of surgical risk, temporal lobe AVM was determined as grade I, parietal lobe AVM – grade III. There were no focal neurological symptoms. The patient is right-handed, that implies dominant left hemisphere. Ophthalmologic examination showed signs of intracranial hypertension (ICH) (moderate swelling of optic nerve discs).

Anamnestic data and examination of the patient did not show the abnormalities typical for hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease, Wyburn-Mason syndrome) and other syndromes associated with AVM.

Stage-by-stage microsurgical resection of both AVMs was offered considering high cumulative risk of rupture of two malformations in a young patient, signs of ICH and manifestation with a generalized epileptic seizure. We considered that left temporal AVM was characterized by higher risk of hemorrhage due to less dimensions. Therefore, resection of this AVM was carried out at the first stage.

Surgery 1. Left-sided pterional craniotomy was followed by visualization of Sylvian fissure. Afferent arteries of AVM from the left MCA were coagulated and intersected. Left temporal AVM was mobilized. At the final stage, the vein draining AVM into the left transverse sinus was crossed. Postoperative period was uneventful. There were no focal neurological symptoms.

Ophthalmologist did not reveal clear signs of ICH regression compared to preoperative data.

After a month, the patient was prepared for the second surgical stage. A combined intervention was performed.

Surgery 2. Initially, endovascular partial embolization of the left parietal lobe AVM was performed. The purpose of surgery was occlusion of the deep afferent artery originating from the left PCA. Occlusion was achieved through selective embolization of the afferent vessel with Trufill n-BCA adhesive composition 0.6 ml (Codman & Shurtleff, Inc., USA) in a dilution with ethiodol 1:1. There were no complications after endovascular surgery.

Surgery 3. Microsurgical resection of a partially embolized left parietal AVM was performed the next day. Linear skin incision was followed by craniotomy in the left parietal-parasagittal region. It was found that the AVM drainage vein was significantly enlarged before confluence with superior sagittal sinus and compressed a bone (indentation 2×2 cm) (Fig. 3). Patent afferent vessels from the left MCA and pericallosal artery were coagulated and intersected. Angiomatosis focus extending towards posterior horn of the left lateral ventricle was found near the basal pole of AVM. In this area, resection of AVM was associated with moderate bleeding. Nevertheless, overall intraoperative blood loss was trivial (up to 200 ml).

Mental disorders (disorientation, emotional lability, reduced criticism) occurred in postoperative period. Thus, therapy with antipsychotics was required. Ophthalmological examination after 5 days revealed visual field impairment (right-sided homonymous hemianopsia). According CAG data, no patent AVM remnants were observed (Fig. 4).

The patient was discharged after 9 days. Mental disorders regressed at discharge. Follow-up survey in 35 days after the last surgery revealed no cognitive impairment or focal neurological symptoms. No epileptic seizures were observed within the follow-up period. Regression of optic nerve swelling and right-sided homonymous hemianopsia was also noted.

Discussion

It is difficult to find a comprehensive definition of the term “multiple brain AVM” in the literature. Some authors attribute to this group combination of typical AVMs with X-ray negative AVMs. The last ones are detected during CAG only after resection of the first malformation. This is associated with blood flow redistribution [8, 10]. In our case, both AVMs were identified prior to treatment, and no malformations de novo were found after resection. It is also important to differentiate true multiple AVMs and AVMs looking like separate vascular nodes after hemorrhage. Moreover, there are initially “multi-chamber” AVMs [8, 11].

Summarizing all features of this disease, we can conclude that multiple AVMs may be determined as two or more clearly defined abnormal vascular nodes separated.
by a visually intact (MRI data) brain parenchyma. Moreover, these AVMs should have (angiography data) different afferent arteries and outflow veins. All these characteristics are present in our patient.

According to the literature, incidence of multiple brain AVMs varies widely. D. Rigamonti et al. analyzed 300 AVMs and found multiple cerebral malformations only in 1 (0.3%) case [12]. According to M.G. Yasargil, multiple brain AVMs made up over 3% [9]. R.A. Willinsky et al. reported a rather high incidence of multiple cerebral AVMs (9%) [8]. However, the authors considered patients with multinodular AVMs and micromalformations appeared in long-term period after resection of primary AVM.

Over the past 10 years (2009—2018), microsurgical resection of brain AVM has been performed in 660 patients at the Burdenko Neurosurgery Center. The reported case of multiple AVMs is the first in this series. Thus, incidence of multiple AVMs in this group is 0.15%. This value is much lower compared to the literature data.

Case reports of multiple cerebral AVMs published since 1985 are summarized in the Table. We included those cases with a detailed description and available angiographic data. Moreover, all these cases corresponded
to our definition of multiple brain AVMs. One of three cases reported by M. Saltman et al. [6] was excluded from the table due to discrepancy with this definition. S. Hasegawa et al. [13], S. Utsuki et al. [10] and L. Manzato et al. [7] reported the adjacent AVM nodes with the same outflow vein. We considered these nodes as one AVM. In this regard, we indicated 3 AVMs in each case instead of 7, 4 and 4 AVMs reported by the authors, respectively. We did not consider combinations with arteriovenous fistula and AVM of the vein of Galen in this table. Thus, we were able to analyze a sample of 21 patients with multiple brain AVMs considering literature data [6, 7, 10, 11, 13, 14—19] and our own observation. Age of patients ranged from 1.5 to 63 years (mean 32.9 years). Incidence of multiple AVMs was similar in males (n=11) and females (n=10). Unilateral multiple AVMs were more common (61.9%, n=13) than bilateral ones (38.1%, n=8). In most cases, multiple AVMs (95.2%, n=20) were localized in different parts of the brain, although they could be supplied through the same vascular pool. Combination of supratentorial and subtentorial multiple AVMs was noted in 6 (28.6%) cases.

In one patient, two cerebral AVMs were more common (71.4%). In some reports, more than 3 AVMs were noted in one patient [10, 13, 20]. A.I. Alomari et al. reported a patient infected with human immunodeficiency virus. This patient had over 7 small vascular malformations with signs of filling the veins in arterial phase [21]. These malformations were atypical. Undoubtedly, each of these cases requires more comprehensive analysis to understand the pathogenetic differences from true brain AVMs.

Some authors demonstrated the relationship of multiple cerebral AVMs with other diseases: Osler-Weber-Rendu disease, Wyburn–Mason syndrome [8, 22]. Osler-Weber-Rendu disease (or hereditary hemorrhagic telangiectasia) is characterized by multiple telangiectasias on nasopharyngeal mucous face and body. These telangiectasias can cause hemorrhagic events and secondary anemia. Incidence of multiple cerebral AVMs may be up to 28% in patients with Osler-Weber-Rendu disease [22].

As follows from the table, AVM-related hemorrhage was the reason for examination in the majority (71.4%) of patients. As a rule, concomitant AVMs were unruptured. Hemorrhage from both AVMs is presented in few cases [8, 21]. S. Utsuki et al. reported a patient admitted to the hospital with intracerebral hematoma in the left frontal lobe due to AVM rupture. Resection of this AVM and debridement of hematoma were followed by hemorrhage from the AVM in the left temporal lobe after 10 days. Thus, early surgical intervention was required. The authors associated hemorrhage from the second AVM with increased “hemodynamic load” as a result of blood flow redistribution [10].

These data make us think about priority and time of surgical treatment of patients with multiple AVMs. Most authors prefer AVM with signs of hemorrhage for the first stage of surgical treatment. Method and time of treatment of the second AVM are individualized.

According to the table, microsurgical treatment of patients with multiple cerebral AVMs was divided into stages with interval from 1 week to 7 months [6, 10, 14—16, 17, 18]. Perhaps, clinicians, as well as we in our case, suggested that simultaneous microsurgical intervention for both AVMs may be traumatic and associated with higher risk of neurological complications.

In our case, AVM manifested with epileptic seizure, and there were no MR signs of hemorrhage. In this regard, treatment strategy was based on the principles of treatment of unruptured single AVMs [23]. High cumulative annual risk of hemorrhage associated with young age of the patient was essential. In our opinion, treatment of multiple AVMs in patients with favorable surgical angiarchitectonics and localization of malformations should not be postponed for a long time after diagnosis. Other authors adhere to the same approach [11, 15, 24]. Sequence of AVM resection was also determined by predictors of rupture (dimension of malformation in this case) [25]. We assumed that resection of a larger AVM in the parietal lobe would be followed by increased hemodynamic load on other cerebral vessels including a small AVM in early postoperative period. This phenomenon has also been previously described [26]. Therefore, resection of a smaller AVM in the temporal lobe was performed first.

**Conclusion**

Multiple brain AVMs is a rare disease. According to our data, multiple AVMs make up 0.15% of all patients eligible for surgery. In our case, microsurgical staged resection of both AVMs combined with preliminary endovascular embolization of a more complex AVM was a radical approach ensured favorable clinical outcome.

**Authors’ participation:**

Concept and design of the study — Yu.P.


Writing the text — Yu.P., V.G.

Editing — Sh.E.

The authors declare no conflicts of interest.
### Literature data on patients with multiple arteriovenous malformations

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patient</th>
<th>Age, gender</th>
<th>Localization of AVM</th>
<th>Symptoms</th>
<th>Treatment approach</th>
<th>Time between treatment stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Zellem et al., 1985 [14]</td>
<td>1</td>
<td>36; f</td>
<td>1) FL (L); 2) FL (L)</td>
<td>Non-specific symptoms</td>
<td>1) MS</td>
<td>7 months</td>
</tr>
<tr>
<td>T. Tada et al., 1986 [15]</td>
<td>2</td>
<td>1,5; f</td>
<td>1) OL (R); 2) Cerebellum (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS</td>
<td>1.5 months</td>
</tr>
<tr>
<td>K. Reddy et al., 1987 [16]</td>
<td>3</td>
<td>16; f</td>
<td>1) FL (R); 2) TL (R); 3) PL (L)</td>
<td>Epilepsy</td>
<td>1) MS</td>
<td>1 week between each stage</td>
</tr>
<tr>
<td>D. Fong., S.T. Chan, 1988 [24]</td>
<td>4</td>
<td>16; f</td>
<td>1) TL (R); 2) TL (L)</td>
<td>Hemorrhage from both AVMs</td>
<td>1) MS</td>
<td>7 years</td>
</tr>
<tr>
<td>Y. Nakayama et al., 1989 [17]</td>
<td>5</td>
<td>40; m</td>
<td>1) PL (L); 2) Insular lobe (L)</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS</td>
<td>1 month</td>
</tr>
<tr>
<td>K. Reddy et al., 1987 [16]</td>
<td>6</td>
<td>37; f</td>
<td>1) Pons 2) OL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>E. Kohmura et al., 1990 [18]</td>
<td>7</td>
<td>23; m</td>
<td>1) Subcortical nuclei (L); 2) Sphenium of corpus callosum</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS 2) MS</td>
<td>1.5 months</td>
</tr>
<tr>
<td>M. Salcman et al., 1992 [6]</td>
<td>8</td>
<td>42; f</td>
<td>1) TL (L); 2) PL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS</td>
<td>3 months</td>
</tr>
<tr>
<td>S. Hasegawa et al., 1999 [13]</td>
<td>9</td>
<td>49; f</td>
<td>1) FL (R); 2) TL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>Y. Nakayama et al., 1989 [17]</td>
<td>10</td>
<td>22; m</td>
<td>1) OL (L); 2) FL (R); 3) TL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS 2) MS</td>
<td>—</td>
</tr>
<tr>
<td>M. Salcman et al., 1992 [6]</td>
<td>11</td>
<td>47; m</td>
<td>1) FL (L); 2) TL (L); 3) PL (L)</td>
<td>Hemorrhage from two AVMs</td>
<td>1) MS</td>
<td>10 days between MS</td>
</tr>
<tr>
<td>Y. Miyasaka et al., 2003 [19]</td>
<td>12</td>
<td>50; f</td>
<td>1) FL (R); 2) PL (R); 3) OL (L)</td>
<td>Hemorrhage from one AVM</td>
<td>1) RS 2) RS 3) RS</td>
<td>—</td>
</tr>
<tr>
<td>T. Robert et al., 2016 [11]</td>
<td>13</td>
<td>37; m</td>
<td>1) OL (L); 2) FL (L)</td>
<td>Non-specific symptoms</td>
<td>1) Follow-up 2) Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>L. Manzato et al., 2017 [7]</td>
<td>14</td>
<td>49; m</td>
<td>1) Midbrain (R); 2) FL (L)</td>
<td>Hemorrhage from aneurysm</td>
<td>Without surgery</td>
<td>—</td>
</tr>
<tr>
<td>T. Robert et al., 2016 [11]</td>
<td>15</td>
<td>24; m</td>
<td>1) FL (L); 2) Subcortical nuclei (L)</td>
<td>Hemorrhage from both AVMs</td>
<td>1) MS 2) RS</td>
<td>24 years</td>
</tr>
<tr>
<td>L. Manzato et al., 2017 [7]</td>
<td>16</td>
<td>20; m</td>
<td>1) PL (R); 2) Midbrain (L)</td>
<td>Non-specific symptoms</td>
<td>1) EE Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>L. Manzato et al., 2017 [7]</td>
<td>17</td>
<td>63; f</td>
<td>1) FL (L); 2) Cerebellum (R); 3) Midbrain (L)</td>
<td>Hemorrhage from one AVM</td>
<td>1) EE 2) Follow-up 3) Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>L. Manzato et al., 2017 [7]</td>
<td>18</td>
<td>63; m</td>
<td>1) FL (L); 2) Cerebellum (L)</td>
<td>Non-specific symptoms</td>
<td>1) Follow-up 2) Follow-up</td>
<td>—</td>
</tr>
<tr>
<td>L. Manzato et al., 2017 [7]</td>
<td>19</td>
<td>17; f</td>
<td>1) PL (R); 2) OL (R); 3) OL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) EE 2) EE 3) EE</td>
<td>3 months between each stage</td>
</tr>
<tr>
<td>Our case</td>
<td>20</td>
<td>13; m</td>
<td>1) PL (R); 2) OL (R)</td>
<td>Hemorrhage from one AVM</td>
<td>1) MS 2) EE</td>
<td>Within the same day</td>
</tr>
<tr>
<td>Our case</td>
<td>21</td>
<td>26; m</td>
<td>1) TL (L); 2) PL (L)</td>
<td>Epilepsy</td>
<td>1) MS 2) EE+MS</td>
<td>1 month</td>
</tr>
</tbody>
</table>

Note: FL — frontal lobe; TL — temporal lobe; PL — parietal lobe; OL — occipital lobe; (L) — left; (R) — right; MS — microsurgical resection, RS — radiosurgery, EE — endovascular embolization.
This manuscript is devoted to the management of a rare disease — multiple cerebral arteriovenous malformations (AVMs). The report is valuable since the authors discuss not only own clinical observation, but also literature data on the treatment of 21 patients with AVM. There are few data on multiple AVMs in the world neurosurgical literature. Thus, various questions regarding classification and treatment remain open.

First of all, I would like to note that the authors set the task to define the concept of “multiple AVMs”. They clearly answered this question considering imaging data on angioarchitecture of AVMs.

Very controversial questions are also formulated. What AVM should be corrected first? What treatment strategy is preferable?

Considering literature data, the authors concluded that multiple AVMs are usually diagnosed after hemorrhage. In this case, hemorrhage-responsible AVM requires resection first. However, what strategy is desirable if there were no hemorrhages from AVM? Smaller AVMs are known to have a higher risk of rupture. Accordingly, the authors correctly resected smaller AVM in the left temporal lobe first. Correction of a larger AVM was performed using endovascular embolization followed by microsurgical resection. According to the modern data, this approach improves quality of resection and safety of surgical treatment. The use of only one of method (microsurgical or endovascular) for the treatment of complex AVMs inevitably leads to significantly increased risk of complications.

In patients with unruptured multiple AVMs, various factors associated with increased risk of rupture should be considered besides AVM dimensions to determine sequence of resection (intraneurysms, efferent vein stenosis, deep venous drainage, single drainage vein, direct shunts inside the AVM and other factors).

Possible summation of gradations of each AVM is an interesting question. Treatment of multiple AVMs is undoubtedly a more difficult problem and associated with increased risk of complications. However, summation of AVM gradations is not entirely correct since the total score may exceed maximum Spetzler – Martin grade 5 (for example, in a patient with 3 nodes and grade 2 or 3 for each node). Perhaps, it makes sense to evaluate AVM resection complexity grade in another fashion. The newly developed scale or complexity of resection of each node individually may be applied for this purpose. Of course, this issue requires further discussion by specialists in AVM treatment.

Thus, this issue and above-described case report of successful staged combined surgical treatment of multiple AVMs are of great interest and show the possibilities of modern approaches to the treatment of this pathology.

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Perimedullary arteriovenous fistula. Case report and literature review

© M.O. Demin, A.R. Tekoev, Yu.V. Kushel

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Abstract

Arteriovenous fistula is a common vascular abnormality of spinal cord and meninges. This disease is more common in young men. Clinical manifestation includes progressive sensitive and motor disorders. However, acute symptoms including impaired consciousness, head or back pain are also possible. The authors describe a rare case. A 15-year-old boy experienced acute depression of consciousness accompanied by headache, vomiting, weakness in the upper limbs and sensitive disorders. The patient was hospitalized to the intensive care unit and examined for subarachnoid hemorrhage. MRI of the head and cervical spine and direct invasive angiography were performed. Perimedullary AVF of cervical spinal cord was diagnosed. Complete clinical regression was observed within a month. Microsurgical removal of AVF was performed in scheduled fashion. Postoperative follow-up period was over 6 months.

Keywords: spinal AVF, SAH, pediatric neurosurgery, endovascular, embolization, microsurgery, vascular neurosurgery, spine surgery, laminotomy.

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Abbreviations:

AVF — arteriovenous fistula
AVM — arteriovenous malformation
CT — computed tomography
MRI — magnetic resonance imaging
SAH — subarachnoid hemorrhage
Vascular malformations make up ≤5% of all spinal cord diseases. However, AVMs are the most common vascular anomalies of spinal cord and its sheaths [1]. Seven classifications of spinal arteriovenous abnormalities have been proposed since 1971 [2]. According to the most famous modified classification of R.F. Spetzler [3], arteriovenous malformations (AVM) and arteriovenous fistulae (AVF) of spinal cord are distinguished in addition to vascular neoplasms and aneurysms. AVFs are divided into extradural, intradural and extradural ventral (with one or more sources of blood supply). AVMs are divided into extra-intradural and intradural ones (intramedullary, compact, diffuse, and AVM of medullary cone). Depending on angioarchitectonics, perimedullary fistulae are divided into 3 types: type A — one afferent artery, low blood flow through the fistula, moderate enlargement of the veins; type B — medium-sized fistula with several afferent arteries as a rule and more significant vein dilation compared to type A; type C — large fistula with multiple afferent arteries, high blood flow and significant enlargement of venous system.

In 2017, K. Takai [2] proposed to classify spinal cord AVMs depending on their relation to the dura mater (dural, intra- and extradural) and type of drainage (fistula and malformation).

According to the literature, perimedullary AVFs are more common in males aged 30—40 years. AVF can occur at any level from large occipital foramen to sacral region. However, fistula is more common at the thoracic and lumbar spinal cord level (up to 90%). Incidence is less than 10% for cervical and sacral levels [4, 5].

Symptoms of perimedullary AVFs are usually caused by progressive compression myelopathy or circulatory steal-syndrome followed by myelopathy (pain, sensitivity disorders, motor disorders) [4, 5]. An acute course (hemorrhage) is less common. This event results a headache, impaired consciousness, back pain, meningeal or focal symptoms [6—8]. According to G.J. Hankey and M.R. Nelson [9], cerebral symptoms were observed in 80% of patients with spinal subarachnoid hemorrhage (headache — 70%, impaired consciousness — 22%). In this case, severity of a headache may be similar to that in aneurysmal SAH. According to S. Cullen et al. [10], AVF is more prone to hemorrhage in childhood. There are several case reports on acute hemi- and tetraparesis on the background of complete well-being [11, 12].

According to M.J. Vermeulen et al. [13], spinal AVF cause cerebral SAH in less than 5% of cases. Searching for the cause of SAH is difficult in these cases [14]. Routine CT upon admission can reliably confirm the fact of SAH. Nevertheless, a cause of hemorrhage may be unclear.

Diagnosis of AVF includes magnetic resonance imaging (MRI) or CT angiography, direct angiography [15]. Spinal cord can appear hypointense in T1WIs due to compression and venous congestion with edema. In T2WIs (including CISS, FIESTA, TSE), a hyperintense signal is detected due to spinal cord edema. Moreover, enlarged and convoluted veins are observed. Their diameter significantly exceeds that of afferent vessels. Subtraction angiography is valuable to determine an afferent artery. Differential diagnosis of AVF is carried out with degenerative spine diseases, polyneuropathies, tumors.

Management of AVF required closure of arteriovenous fistula [16, 17]. Microsurgery or endovascular embolization may be applied [10]. A combination of these methods is also possible [18].

There is an extensive experience in endovascular treatment of vascular spinal diseases at the Burdenko Neurosurgery Center [19]. Therefore, this approach is traditionally preferable. However, optimal strategy is still a matter of debate in other hospitals. Intraoperative fluorescence during direct interventions [20] ensures accurate analysis of an afferent artery and control of fistula closure. Complications after open surgery are pseudomeningocele, CSF leakage with infectious adverse events, spinal column deformation and instability. Endovascular approach is associated with higher risk of spinal cord ischemia and recanalization of a fistula in addition to technical difficulties (tortuosity and small diameter of an afferent vessel, risk of vascular dissection). According to R.V. Phadke et al. [21], endovascular treatment of AVF type A and B was ineffective in 40% of cases due to tortuosity and small dimensions of afferent artery. In such cases, microsurgery ensures direct closure or excision of a fistula under visual control. However, endovascular treatment of AVF type B and C (“adhesive” composition, microcoils, “onyx” and their combinations) is considered first-line treatment [22].

Case report

We report a rare case of left-sided perimedullary dorsal AVF at the cervical level (CIV—CV) in a 15-year-old man. Symptoms were acute vomiting with headache, impaired consciousness, weakness in the upper limbs and sensitivity disorder. The patient with these complaints was hospitalized at the ICU in May 2018 and intubated. MRI of the brain and cervical spinal cord, MR angiography and direct angiography were performed the next day. Perimedullary AVF was diagnosed. Most likely, blood supply occurred through the left radicular artery (CV — CVI) (Fig. 1, 2).

Symptoms completely regressed within 3 weeks. The patient admitted to the pediatric department of the Burdenko Neurosurgery Center in 4 months after SAH. There were no preoperative complaints. Microsurgical resection of perimedullary CIV — CV AVF was performed on September 13, 2018. Hypertrophied vessels are clearly visible in intraoperative images (Fig. 3, 4).

The child was transferred to pediatric department after surgery. Postoperative period was uneventful. For several days, the patient complained of pain within a wound and numbness of the left hand and was discharged in 4
days after surgery. There were no MR and angiographic data on AVF (fistula, dilated veins) after 8 months (Fig. 5-7). Sensory impairment in the left hand regressed.

Discussion

Perimedullary spinal AVF is a rare vascular disease. Untimely diagnosis and treatment are fraught with disabling consequences. Meningism and cerebral symptoms can occur in intracranial and spinal hemorrhages. In the last case, focal neurological syndrome can become a diagnostic criterion. Accurate analysis of focal deficit may be valuable to assume the level of damage.

In our case, perimedullary AVF manifested with general cerebral (headache with vomiting and impaired consciousness) and focal symptoms (segmental sensitivity disorders and mild upper limb paresis). Timely MRI of the brain and cervical spinal cord, as well as angiography, made it possible to identify a cause and localization of SAH. Cautery of an afferent artery and enlarged efferent veins was carried out during microsurgical intervention under direct visual control.

Authors’ participation:
Concept and design of the study — Yu.K., M.D.
Collection and analysis of data — M.D., A.T.
Writing the text — M.D.
Editing — Yu.K.

The authors declare no conflicts of interest.
REFERENCES


Commentary

The authors reported an interesting case of microsurgical treatment of perimedullary arteriovenous fistula of cervical spinal cord in a young man. AVF manifested with subarachnoid hemorrhage. A relevance of this manuscript is obvious since subarachnoid hemorrhage is traditionally considered as a sign of intracranial vascular lesion as a rule. However, it is necessary to clarify the features of spinal vascular malformations. The authors refer to the report of M.Y. Akgun et al. The last ones emphasized predominant manifestation of disease due to compression myelopathy or circulatory steal-syndrome followed by myelopathy. At the same time, the authors describe the course of spinal dural AVF. It should be noted that perimedullary AVF occurs mainly in young patients or even in childhood and more often manifest with subarachnoid hemorrhage. “Steal-syndrome” is more common for ventral perimedullary fistulae in anterior spinal artery pool. Intramedullary AVM is usually accompanied by hemorrhage into spinal cord matter. Thus, vascular lesion of the spinal cord may be supposed in accordance with clinical features of disease.

Planning of surgical intervention and prediction of further course are based on MRI and CT angiography data. However, the final decision on the structure of malformation should be based on direct spinal angiography data. This method is valuable to identify AVF and arteries supplying spinal cord matter since other methods have lower resolution.

Concerning the advantages and disadvantages of microsurgical and endovascular approaches, it should be emphasized that a combined approach is preferable for this formidable disease in the world literature.

A competent approach to the diagnosis and treatment is described in clinical observation. Regarding the causes of postoperative transient myelopathy, one can assume that it is associated with excision of enlarged veins combined with increased CV, CVI, CVII kyphosis. Further follow-up is required. This case report is very interesting for neurosurgeons and other specialists encountering subarachnoid hemorrhages and meningitis.

E.V. Vinogradov (Moscow, Russia)
Commentary

The manuscript is devoted to a rare spinal cord vascular lesion — perimedullary arteriovenous fistula (AVF) followed by symptoms of intracerebral subarachnoid hemorrhage. This clinical course of spinal AVF is a phenomenon complicating fast diagnosis.

The authors report a literature review and clinical case. The review is devoted to epidemiology, clinical course, differential diagnosis and surgical treatment of spinal AVF. Advantages and disadvantages of endovascular and microsurgical treatment, postoperative outcomes and complications are discussed. The authors emphasize “atypical” symptoms for spinal cord vascular lesion in a patient (acute headache with impaired consciousness). Case report is well illustrated by neuroimaging data and intraoperative images.

Atypical clinical manifestations of spinal vascular lesion (intracerebral subarachnoid hemorrhage) are emphasized in the manuscript. This report will be valuable for neurosurgeons, neurologists, radiologists

A.S. Saribekyan (Moscow, Russia)
navigation in vascular neurosurgery

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Abstract

Literature review is devoted to the role of frameless neuronavigation in surgery of distal aneurysms, cavernomas, arteriovenous malformations, Kimmerle’s anomaly and revascularization surgeries. Visualization methods used in preoperative preparation of patients with vascular lesions compatible with frameless neuronavigation and the methods of intraoperative visualization as an addition to navigation are described.

Keywords: minimally invasive surgery, frameless neuronavigation, distal aneurysms, cavernomas, arteriovenous malformations, Kimmerle’s anomaly, extra-intracranial bypass, intraoperative sonography.

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Abbreviations
KS — Karnofsky score
NSCLC — non-small cell lung cancer
TFD — total focal dose
CHT — chemotherapy
DS-GPA — diagnosis-specific GPA
GPA — Graded Prognostic Assessment
MS — median survival
QALY — quality-adjusted life-year
QUARTZ — quality of life after radiotherapy for brain metastases
RTOG — Radiation Therapy Oncology Group
WBRT — whole-brain radiotherapy
Frameless neuronavigation systems in neurosurgery improved an accuracy of surgical interventions and extended the indications for various minimally invasive procedures. Initially, frameless neuronavigation system was used in tumor resection for determining the optimal point for craniotomy and clarifying the boundaries of tumor. The research of R. Watanabe et al. was followed by widespread introduction of neuronavigation systems into neurosurgical practice including aneurysm clipping, excision of arteriovenous malformations (AVMs) and cavernomas [1, 2]. Neuronavigation is valuable for navigation in complex vascular anatomy, planning of localization, trajectory and depth of surgical approach, dimensions of craniotomy. Therefore, improved intraoperative accuracy reduces the risk of intraoperative complications. However, neuronavigation-assisted vascular neurosurgery requires further analysis despite the available literature data.

**Surgical treatment of distal brain aneurysms**

Open surgery is preferred for distal cerebral aneurysms. Clipping of the aneurysms is the most common procedure [1, 2].

Currently, real-time combination of preoperative neuroimaging data and intraoperative situation is required to improve the accuracy of surgery for distal aneurysms (DA). CT AG is preferred for DA visualization. Unlike digital subtraction angiography, CT angiography ensures 3D modeling of the aneurysm. This technique improves an assessment of aneurysm dimension, configuration, features of aneurysmal sac and neck, thrombotic masses and atherosclerotic changes in the cavity and neck of the aneurysm, relationship with adjacent vessels and bone structures. These data are essential for better understanding of anatomy. In addition, CT AG can be used as a visualization method for neuronavigation [3, 4].

T. Kim et al. (2007) reported DA clipping using frameless neuronavigation (Brain LAB, Germany). There were 12 patients (9 women, 3 men) with anterior cerebral artery aneurysms for the period 2001—2004. In 10 patients, aneurysms were located in segment A2, segment A3 lesion was observed in 2 patients. Preoperative survey included computed tomography, CT AG. Registration was carried out using radiopaque labels. Registration accuracy was 0.5—1.5 mm. Intraoperative accuracy was not determined. The authors determined the optimal craniotomy, its dimensions and trajectory for approaching aneurysms using the navigation system. There were no intraoperative technical problems. Neuronavigation ensured diagnosis of aneurysms in all 12 patients. There were no cases of intraoperative rupture [5].

J.-S. Kil et al. clipped 32 aneurysms using keyhole-approach and frameless neuronavigation for the period 2008—2010. The authors marked skin incision with a length of 4—5 cm and craniotomy 2.5×4 cm. Dura mater dissection was followed by analysis of actual localization of the aneurysm and optimal surgical trajectory using frameless neuronavigation. Then, operations were continued using traditional microsurgical techniques. Mean surgery time was 2.19 hours (range 100—150 min) [6].

E. J. Hermann et al. (2015) operated on 8 patients (5 women, 3 men) with DA of ACA. Four patients had aneurysm of pericallosal and callosomarginal artery bifurcation, two patients — aneurysm of segment A2 and one patient — aneurysm of segments A3—A4. One patient had multiple distal aneurysms of ACA within the bifurcation of pericallosal and callosomarginal arteries, as well as aneurysms of A2 segment. Preoperative CT AG was performed in all patients, and these data were transferred to the navigation system. Registration deviations were less than 2 mm. An exception was one patient with deviation about 5 mm from the target point due to displacement of the anatomical landmarks after surgical dissection [7].

M.R. Onen et al. (2018) described successful clipping of aneurysms of the M3 segment of the middle cerebral artery (CMA) using a navigation system. The authors emphasized that frameless neuronavigation ensured surgical approach with minimal impact on adjacent surrounding tissues and vessels of the brain. In authors’ opinion, the disadvantages of neuronavigation are high risk of postoperative infection, moderate accuracy of neuronavigation in identifying the aneurysms after CSF drainage from subarachnoid space and brain ventricles, and increased cost of intervention. The authors proposed intraoperative sonography to compensate navigation errors [8].

S.H. Lee et al. (2007) reported a rare clinical case of surgical treatment of a patient with DA of M4 segment of the right MCA combined with ipsilateral ICA thrombosis. Left-side hemiparesis of the arm (2 points) and leg (3 points), as well as speech disorders appeared 5 days before admission. MRI revealed ischemic focus in the right MCA, MR AG — right ICA occlusion. Cerebral angiography was performed, and fusiform aneurysm of M4 segment of MCA within 18.9 mm from the cortex was diagnosed. Neuronavigation-assisted resection of the aneurysm was followed by extra-intracranial bypass surgery. The authors emphasized that frameless neuronavigation made it possible to determine localization of the aneurysm, perform surgical approach through the fissure and avoid corticotomy [9].

I. Cabrilo et al. (2014) clipped 39 unruptured aneurysms using neuronavigation system. One patient had DA of M2 segment of MCA, other proximal aneurysms were localized in the ICA and MCA pools. Preoperative survey included MR AG and CT AG of intracranial vessels, digital subtraction angiography, MRI and CT of the brain. The operating microscope was intraoperatively synchronized with neuronavigation. The contours of the object of interest were projected into the microscope's field of view using a special unit in the microscope in Image Injection mode and Heads-Up Display (HUD) augmented reality function in the navigation system. This image was transparent. Thus, both the region per se and the projected image were visualized. This technique was valuable to de-
termine the optimal surgical trajectory to all aneurysms, avoid large traumatic skin incisions and craniotomies, and minimize subarachnoid dissection in 65% of cases [10].

P. Marinho et al. (2012) indicate an effectiveness of HUD for intraoperative aneurysm rupture and clipping [11]. T. Toyooka et al. clipped 35 unruptured aneurysms using HUD for the period from 2014 to 2016. The control group retrospectively consisted of 41 patients who were operated on for the period 2012—2014 without this technology. Standard craniotomy was carried out in 15 patients from the HUD group and 20 patients from the retrospective group. Mini–craniotomy was performed in 20 patients from the HUD group and 21 patients from the control group. Duration of surgery through mini–craniotomy was similar in both groups (202±42 and 192±41 min, respectively). Dimension of standard craniotomy was less in the HUD group (pterional approach — 20×26 mm, suboccipital approach — 21×28 mm) compared to the control group (pterional approach — 25×30 mm, suboccipital approach — 27×30 mm). Dimensions of mini–craniotomy also differed in both groups: in patients of the “HUD” group with pterional approach — 18×25 mm, suboccipital approach — 19×22 mm; in patients of the control group with pterional approach — 21×28 mm, suboccipital approach — 20×28 mm [12].

**Surgical treatment of brain AVM**

Surgical resection of AVM is still the most adequate and effective treatment option despite the development of endovascular methods and radiosurgery. S.M. Russell et al. (2002) retrospectively analyzed 44 patients with AVM divided into 2 groups. The 1st group included 22 patients (standard surgical techniques), the 2nd group (n=22) — frameless neuronavigation. Preoperative survey included MRI in all patients, the obtained data were loaded into the neuronavigation system. Registration was carried out using radiopaque labels, deviation did not exceed 2 mm. AVM localization, optimal dimensions of craniotomy and skin incision, and optimal approach to AVM were determined using neuronavigation. Surgery time was 497 (189±332) min in the 1st group and 290 (136±502) min in the 2nd group. Blood loss was 657 (100±1250) ml in the 1st group and 311 (50±800) ml in the 2nd group. In the 1st group, postoperative complications developed in 3 patients: hemorrhage from residual part of AVM, visual disturbances, oculomotor nerve paralysis followed by functional recovery after 4 months. Postoperative complications were also noted in the 2nd group. Hemiparesis occurred in 1 patient while there were no imaging data on hemorrhage or residual fragment of AVM. Another patient had trochlear nerve paresis with complete recovery after 3 weeks. In the 3rd patient, postoperative imaging data on hemorrhage without residual AVM were obtained that was recognized as hemorrhagic impregnation. The authors suggested to use different neuroimaging methods combined with neuronavigation depending on the characteristics and localization of AVM. For example, MRI was proposed for deep supratentorial AVM, as well as AVM localized in functionally significant zones. CT and CT AG are preferable for skull base and infratentorial AVMs [13]. The advantages of CT and CT AG are 3D-modeling and visualization of the afferent arteries, veins and bone landmarks. The advantage of MRI is excellent visualization of brain tissue, MR AG — analysis of blood flow velocity and direction in AVM vessels that is impossible in CT AG [13, 14].

I. Cabrilo et al. (2014) resected AVMs in 5 patients using neuronavigation (Kolibri Brain LAB, Germany) and HUD. Preoperative survey consisted of CT AG and MR AG of the brain. Imaging data were transferred to neuronavigation system for 3D-modeing. Then, the operating microscope was synchronized with neuronavigation. The authors emphasized the effectiveness of navigation and HUD for marking craniotomy and skin incision depending on localization and dimensions of AVM. However, in authors’ opinion, these technologies do not allow identification of afferent arteries due to their complex vascular architectonics [15]. At the same time, G. Unsgaard et al., J.S Walkden et al. argue that frameless neuronavigation combined with 3D ultrasound angiography ensures identifying superficial and deep efferent vessels, evaluation of AVM dimensions and its residual fragments [16, 17].

E.M. Berntsen et al. (2009) described resection of AVM localized within primary motor cortex. Functional MRI, MR tractography and MR AG were carried out in preoperative period. These data were uploaded to the workstation. Neuronavigation system with preoperative imaging data combined with intraoperative sonography was valuable to identify vascular lesion, determine optimal approach, improve intraoperative accuracy and reduce the risk of neurological complications [18].

Accurate preoperative identification of functionally significant areas is an important aspect due to undesirable intraoperative lesion of these zones. In this case, fMRI is justified to determine the dominant speech hemisphere. Undoubtedly, fMRI is very important in preoperative survey. However, this method is sensitive to changes in local blood flow and brain tissue metabolism within the AVM region associated with its hemodynamic peculiarities (for example, steal-phenomenon). These features can influence fMRI data [19, 20].

R.E. Latchaw et al. proposed electrocorticography, positron emission tomography and magnetocencephalography as alternatives to fMRI [21].

Intraoperative sonography is valuable to identify afferent and efferent vessels for intraoperative confirmation of total AVM resection and visualization of hematomas occurring during AVM resection. H. Xu et al. (2017) reported AVM resection in 41 patients using intraoperative sonography (21 men, 20 women). Intraoperative sonography after craniotomy was used in all cases. The authors concluded that ultrasound im-
aging simplified intraoperative analysis of vascular anatomy. Moreover, Doppler mapping ensured visualization of shape and edges of AVM, afferent arteries and drainage veins [22].

Surgical treatment of patients with brain cavernoma

One of the most important principles in surgery of cavernous malformations (CM) is adequate, minimally invasive approach ensuing minimally traumatic resection of the cavernoma through a narrow surgical pathway. Preoperative and intraoperative survey includes MRI, fMRI, MR tractography.

D. Winkler et al. (2004) reported neuronavigation-assisted treatment of 21 patients with brain cavernomas. Nine patients had tumor of temporal lobe, 6 — occipital lobe, 3 — frontal lobe, 1 — parietal lobe, 1 — corpus callosum, 1 — ventricular system. Lesion of functionally significant zones was observed in 5 cases: 2 — precentral gyrus, 2 — postcentral gyrus, 1 — speech center. The authors reported superficial (less than 2 cm from the cortical surface) and deep (over 2 cm from the cortical surface) cavernomas. Dimensions of cavernomas varied from 5 to 60 mm (mean 25.7 mm). All cavernomas were successfully resected. Favorable postoperative outcomes and total resection were confirmed in all patients [23].

A.M. Mukha (2017) reported neuronavigation and intraoperative sonography in surgical treatment of patients with CM. There were 62 patients for the period from 2005 to 2014 (27 women, 35 men). Preoperative survey included MRI and fMRI. Neuronavigation was intraoperatively used in 49 patients with supratentorial and cerebellar CM. In 2 patients, neuronavigation was not used due to unverified preoperative diagnosis and suspected hemorrhagic stroke. Intraoperative sonography was used in 6 patients with intraoperative hemorrhage. In all cases, neuronavigation and intraoperative sonography were valuable for resection of CM and intracerebral hematoma debridement [24].

T. Okada et al., M. Kinoshita et al., S. Nimsky et al. emphasized that intraoperative MR tractography for focal brain lesions can disorient the neurosurgeon, since the dimensions and localization of pathways are not accurately estimated. This is due to brain displacement during resection that results the errors in comparison of tractography data with intraoperative imaging [25–27]. In such situations, V.A. Coenen et al. (2005) proposed intraoperative 3D ultrasound with mapping of CM landmarks adjacent to the tract [28]. Other authors propose neuronavigation and MR tractography combined with direct intraoperative stimulation of the tracts for the safest and total resection of cavernoma near functionally significant zones [29, 30].

A. Haberg et al. (2004) emphasized that CM localized at a distance of 10 mm or more (fMRI) data may be resected without the risk of postoperative complications [31].

Intraoperative ultrasound is valuable to adjust navigation model data and objectively assess quality of resection. Transducer with a dimension of 1—3 cm and frequency of 4—8 MHz is preferred for deep lesions and imaging at a depth of 3—8 cm, 10—15 MHz — for superficial CM within 4 cm. As a rule, neurosonography is performed in two perpendicular planes, since imaging of gyri in one plane can be mistaken for a superficial focal lesion [32].

Extra-intracranial bypass surgery with frameless neuronavigation

J.R. Coppens et al. first superimposed EICMA using neuronavigation in 2008. This technique was applied in 2 patients with impaired central perfusion reserve during operations under local anesthesia. Preoperative survey included CT, CT AG. These data were transferred to navigation system and used for marking the branches of superficial temporal artery, M4 segment of MCA, skin incision, and craniotomy. This approach was valuable for suturing the microvascular anastomosis with less invasiveness, accurate skin incision and small craniotomy (20—25 mm) in accordance with the localization of superficial temporal artery and cortical branch of MCA [33].

I. Nakagawa et al. (2010) used digital subtraction angiography for 3D modeling in a particular patient. This method ensured EICMA surgery through minimally invasive approach in 28 patients [34].

G. Fischer et al. (2009) applied MR AG data for preoperative planning (searching for donor arteries and cortical branch of STA within the Sylvian fissure). As a result, small linear skin incision in the projection of STA and 22-mm mini-craniotomy were performed [35].

Y. Kaku et al. (2012) reported successful extra-intracranial bypass surgery under local anesthesia using 3D CT navigation in 10 patients with severe comorbidities [36]. In 2014, the authors described in detail the algorithm for using a frameless neuronavigation system for extra-intracranial bypass surgery. Preoperative survey included CT and CT AG [37, 38]. Selective EICMA technique was developed in 2017. This method was based on a combination of CT AG and single-photon emission CT using frameless neuronavigation. In this case, 3D modeling based on the above-mentioned survey methods was used for target revascularization of the hypoperfusion region (searching for the donor and recipient arteries in the projection of the hypoperfusion zone). This approach improved brain perfusion in the zone of interest [39].

Surgical treatment of Kimmerle anomaly

The generally accepted approach for Kimmerle anomaly is a median conventional access with incision and dissection of tissues from the occipital tubercle to the CII spinous process. Surgical approach implies advanced dissection of bone structures within the cranio-
vertebral junction from the occipital bone and arch of the axis to the CII—CIII joint. However, this access is characterized by several significant drawbacks: extended skin incision (12 cm), unavailable direct exposure of the bone bridges of Kimmerle anomaly, limited viewing angle and manipulations within the wound, and long-lasting postoperative pain syndrome. These features justified the development of new less invasive intermuscular approach. This technique ensures direct visualization of this lesion through small skin incisions [40, 41].

So, neuronavigation-assisted skin incision for Kimmerle anomaly was proposed at the Sklifosovsky Research Institute for Emergency Care in 2018. This approach ensured more accurate and minimally invasive access to the desired area through small skin incisions. Preoperative CT and CT AG data were uploaded to the workstation. Then, the data were transferred to the neuronavigation system. The last one was used throughout all surgical stages from skin incision marking to bone ring resection. This approach ensured visualization of the compressed V3 segment of the vertebral artery, avoiding large skin incisions and extended bone dissection, minimizing traumatic effect on the cervical spine muscles. As a result, reduced pain syndrome and more favorable cosmetic effect were obtained in postoperative period [42].

Conclusions

Neuronavigation systems are valuable to determine localization of distal aneurysms, arteriovenous malformations, brain cavernomas and Kimmerle anomalies in the absence of bone landmarks. This approach is also effective for preoperative planning of skin incision, craniotomy and optimal trajectory of surgical approach to vascular malformations, donor and recipient vessels in extra-intracranial bypass surgery. However, one should remember that the accuracy of navigation can intraoperatively change due to brain displacement after resection of tumors and malformations, CSF loss. In this case, additional imaging methods (intraoperative sonography) are advisable to compensate the disadvantages of neuronavigation.

Authors’ participation:

Concept and design of the study — A.D.
Collection and analysis of data — E.R.
Writing the text — E.R.
Editing — V.L., I.S.

The authors declare no conflicts of interest.

REFERENCES


The authors declare no conflicts of interest.
The review by V. A. Lukyanchikov and colleagues is devoted to the analysis of the effectiveness of various navigation technologies in surgery of cerebrovascular diseases.

Currently, navigation is a widespread technique in neurosurgical practice. Moreover, this approach is a standard technology for cerebral resection of a brainstem cavernous angioma. Surgical Neurology. 2005;102(4):664-672.

The article is written in a competent scientific language and easy to read. A sufficient number of publications on various neurological forms are analyzed. Reasonable conclusions are made at the end of the manuscript. The article will be interesting, first of all, for residents and postgraduate students, as well as vascular neurosurgeons.

A.L. Krivoshapkin (Novosibirsk, Russia)
Modern trends in diagnosis and surgical treatment of moyamoya disease


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Abstract
This review is devoted to moyamoya disease. It is a rare chronic steno-occlusive cerebrovascular disease. However, moyamoya disease is increasingly diagnosed by neurosurgeons in our country. Unlike atherosclerotic lesions of cerebral arteries, pathogenesis and course of this disease are much more complex and variable. Therefore, specialists often have certain difficulties in diagnosis, management and treatment of these patients. To date, a large number of surgical interventions have been proposed for the treatment of moyamoya disease. Revascularization approaches include direct procedures (extra-intracranial microanastomoses), indirect methods (synangioses) and combined revascularization. The purpose of the review is to systematize current literature data on the pathogenesis, diagnosis, clinical patterns and surgical treatment of patients with moyamoya disease. Results Outcomes of surgical revascularization and the role of its various components in combined approach are under particular attention.

Keywords: moyamoya disease, angiopathy, ischemic stroke, surgical revascularization, combined revascularization, extra-intracranial microanastomosis.

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Abbreviations
ICA — internal carotid artery
PCA — posterior cerebral artery
CT — computed tomography
MRI — magnetic resonance imaging
MR angiography — magnetic resonance angiography
CVA — cerebrovascular accident
ECA — external carotid artery
SPECT — single-photon emission CT
VA — vertebral artery
STA — superficial temporal artery
ACA — anterior cerebral artery
PET — positron emission tomography
MCA — middle cerebral artery
TIA — transient ischemic attack
DM — dura mater
EGPS — encephalagaleo(periosteal)synangiosis
EDAMS — encephalo-duro-arterio-myo-synangiosis
EDAS — encephalo-duro-arterio-synangiosis
EICMA — extra-intracranial microanastomosis
EMS — encephalomyosynangiosis
ASL — arterial spin labeling
CBF — cerebral blood flow
TOF — time of flight
Moyamoya disease is one of the most mysterious cerebrovascular diseases attracting advanced interest of specialists. This disease is special, not like the often diagnosed and well-studied steno-occlusive atherosclerotic lesions of cerebral arteries due to small incidence in our country, complexity of pathogenetic mechanisms and the variety of clinical manifestations. Numerous protocols and clinical guidelines for the management of atherosclerotic steno-occlusive lesions of cerebral arteries are not suitable for patients with moyamoya disease. Moreover, unclear etiology and pathogenesis of disease often lead to the choice of erroneous treatment strategy.

Widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) in our country is associated with more common diagnosis of moyamoya disease in adults and children. At the same time, approaches to the diagnosis and treatment of disease are still unclear; there is a need for their refinement in accordance with the current world experience.

The review is devoted to analysis of current ideas about moyamoya disease, diagnosis and surgical treatment of this lesion.

Moyamoya disease is an idiopathic chronic cerebrovascular disease characterized by progressive bilateral steno-occlusive lesion of distal segments of internal carotid (ICA) and/or proximal parts of middle (MCA) and anterior cerebral arteries (ACA). This lesion is combined with compensatory hypertrophy and enlargement of basal collaterals (hypertrophic lenticulostriate and thalamoperforative arteries). These processes are accompanied by the appearance of a characteristic angiographic sign of contrast-enhanced rete mirabile (“puff of smoke”, moyamoya in Japanese).

Moyamoya disease is a relatively new nosological form that was first described in Japan in the 50s of the twentieth century. K. Shimizu and K. Takeuchi presented the first patient with moyamoya disease at the 14th annual meeting of the Japan Neurosurgical Society (1955). The first manuscript of K. Takeuchi et al. was published in 1957 [1]. Since that time, patients with angiographic vascular changes typical for moyamoya disease have been periodically reported in Japan. At that time, bilateral carotid artery occlusion associated with basal vascular network enlargement was considered as congenital anomaly (like hypoplasia or vascular tumor). In 1963, J. Suzuki et al. reported 6 cases of moyamoya disease at the 22nd annual meeting of the Japan Neurosurgical Society. The authors supposed that enlarged basal vessels developed in response to progressive ICA stenosis for collateral circulation. More importantly, they came to conclusion that the totality of these changes represents a single clinical pathology [2]. In the USA and Europe, the first descriptions of patients with moyamoya disease appeared in 1965 [3, 4]. In 1969, Japanese researchers J. Suzuki and A. Takaku first proposed the term “Moyamoya disease” that later became the generally accepted name of disease. Japanese scientists comprehensively described the pathology, emphasized the progressive nature of disease and distinguished 6 angiographic stages. The last ones are still used around the world to determine the stage of disease [5]. In 1968 and 1969, T. Kudo, A. Nishimoto and S. Takeuchi, along with J. Suzuki and A. Takaku actively published their studies in English-language literature. These researches greatly contributed to recognition of moyamoya disease throughout the world. Therefore, moyamoya disease is called by the names of the authors (Nishimoto-Takeuchi-Kudo disease) in some manuscripts [6, 7].

The epidemiology of moyamoya disease is peculiar. The largest number of cases is detected in Japan, where the prevalence of disease reaches 6–10 per 100,000 and the incidence is 0.54–0.94 per 100,000 [8, 9]. The disease is somewhat less common in China and other Asian countries [10]. In the USA and Europe, moyamoya disease is a rare cerebrovascular lesion since its incidence is several times less. Thus, morbidity in the United States is 0.086 cases per 100,000 [11], in Europe - about 0.03 cases [12]. Incidence and prevalence of moyamoya disease in Russia is presumably similar to European indicators although there are no official data. Epidemiological studies devoted to this disease have not been conducted in our country. There are only few case reports in the national literature [13–20]. To date, there have been no studies on the treatment of large groups of patients with moyamoya disease in Russia. Nevertheless, widespread use of minimally invasive methods for the diagnosis of cerebrovascular lesion and increased awareness of physicians on this disease resulted significantly increased number of patients in recent years including those with asymptomatic course of disease.

Etiology of moyamoya disease is still unclear. Familial nature of disease was established in 10–15% of cases. Therefore, hereditary mechanisms of moyamoya disease were supposed [21, 22]. Various researchers intensively searched for the genes associated with this disease. According to some data, the responsible loci are localized in the 3p, 6p, 17q chromosomes. However, certain genes are still not exactly identified [23]. Considering the recent data, it was suggested that the RNF213 gene at the 17q25-ter locus may be responsible for moyamoya disease in East Asia [24]. Its variant p.R4810K was identified in 95% of patients with a familial form of disease, in 80% of patients with a sporadic form and only in 1.8% of the control group in the Japanese population [24]. It is assumed that adverse environmental factors (autoimmune response, inflammation, infection, hypertension) combined with RNF213 gene polymorphism may be the cause of disease [25]. However, clear correlation between RNF213 gene polymorphism and moyamoya disease has not yet been confirmed in vivo [26].

A feature of moyamoya disease is a steadily progressive course with clear stages of morphological changes in brain vessels. J. Suzuki and A. Takaku described these changes in 1969 [5]. These stages correlate with development of disease in time - from initial ICA bifurcation nar-
rowing to complete restructuring of brain circulation to the system of external carotid arteries (ECA). Specialists consider these processes as a physiological compensatory mechanism (Table 1). At the same time, atherosclerotic or inflammatory changes are not detected in arterial walls. Narrowing is caused by smooth muscle layer proliferation combined with parietal thrombosis. This process is bilateral and affects ICA, MCA and ACA with different rate [27, 28]. Progressive narrowing of the arteries of circle of Willis is followed by collateral blood supply through the small branches of ICA. The network of abnormal small arteries is developed (the so-called moyamoya vessels). These dilated vessels normally supply the optic nerves, pituitary gland, anterior perforated substance, and other skull base and brain structures. These collaterals create a typical angiographic picture of a "puff of smoke".

Conventional clinical manifestations of moyamoya disease are ischemic and hemorrhagic cerebrovascular accidents. There are 2 incidence peaks (at the age of 5–9 years and, somewhat less often, 30–40 years) [8, 29]. The most common type is ischemic with strokes, transient neurological deficit (transient ischemic attacks, TIA), chronic cerebrovascular insufficiency followed by dis-circulatory encephalopathy and paroxysmal symptoms. Ischemic form occurs in most pediatric patients and approximately half of adults [30]. Moreover, the provoking factor of ischemia in children is often hyperventilation caused by crying, playing wind musical instruments or hot food intake [31].

Hemorrhagic form occurs in approximately 30% of cases [32]. The main cause of intracranial hemorrhage is a rupture of brittle collateral moyamoya vessels and sac-cular aneurysms of collateral vessels [33]. It should be noted that intracranial pathways of CBF compensation may be considered pathological, as they lead to ischemic or hemorrhagic symptoms [34, 35]. The timely CBF restructuring to ECA system is essential to avoid severe ischemic and hemorrhagic complications and causes a long (in some cases lifelong) asymptomatic course of disease. The incidence of asymptomatic natural course of moyamoya disease varies from 1.5 to 17.8% [8, 36]. According to various studies, the annual risk of clinical symp-toms (hemorrhage/TIA/stroke) in patients with asymptomatic course of disease is 5.7% [37]. However, risk of stroke occurs in case of insufficient development of extra-intracranial circulation and higher degree of disease progression. In these cases, cerebral perfusion disorders appear in 40% of asymptomatic patients that leads to increased risk of stroke [38]. Surgical treatment is considered in these situations.

Natural course of disease in patients with clinical symptoms is accompanied by significantly increased risk of stroke. According to C.L. Hallemeier et al., repeated ipsilateral stroke occurs in 65% of patients within 5 years [39]. The highest risk of recurrent ischemic stroke is observed in bilateral lesions (up to 82% over 5 years) [39]. The risk of clinical progression within 1 year in children is 35% [40]. T. Kurokawa et al. reported reduced incidence and severity of acute ischemic episodes in children after 4 years of follow-up. However, ischemic encephalopathy grade and neurological deficit are significantly increased [41].

Hemorrhagic course of moyamoya disease is followed by death of almost 20% of patients due to primary intracranial hemorrhage while the risk of recurrent hemorrhage is 38% for 7 years [42] and 61.1% for 27 years [43].

Obviously, such an aggressive course of disease requires timely accurate diagnosis and choice of adequate treatment strategy. The diagnosis is based on the generally accepted angiographic criteria [44]. The last ones were formulated in 1997 using direct angiography data (Table 2). The Guidelines for the Diagnosis and Treatment of Moyamoya Disease (2012) recommended MR angiography and TOF MRI (MRI scanners with magnetic field >1.5 T) for diagnosis of moyamoya disease in addition to direct angiography [45].

The diagnosis of idiopathic moyamoya disease requires to exclude other diseases associated with similar arterial damage. The term "moyamoya syndrome" is used to describe these conditions. The feature of this syndrome is predominantly unilateral arterial lesion. The following diseases are associated with moyamoya syndrome: infections (leptospirosis, tuberculosis), hematologic (sickle cell anemia, cryoglobulinemia, systemic lupus erythematosus), congenital (Down syndrome, Marfan syndrome, tu-berous sclerosis, neurofibromatosis type 1), vascular (atherosclerosis, aortic coarctation, fibromuscular dysplasia), autoimmune (Graves' disease) and other diseases (injuries, previous radiotherapy on the head and neck, radiotherapy of parasellar tumors) [46].

Unlike moyamoya disease, arterial damage in these cases is characterized by more stable clinical picture that significantly affects surgical strategy.

The variety of clinical forms and complexity of pathogenetic mechanisms of moyamoya disease justify high requirements for the diagnostic algorithm. This algorithm is significantly more difficult in contrast to diagnosis of atherosclerotic steno-occlusive cerebrovascular lesions. For example, assessment of brain tissue, collateral blood supply and cerebral perfusion is mandatory.

MRI is a “gold standard” for analysis of structural brain changes [47]. T1, T2 modes (moyamoya vessels are visualized as “flow voids” — signal loss from a moving fluid), FLAIR (severity of ischemic lesions), FIESTA/CISS (reduced ICA outer diameter as a pathognomonic sign of moyamoya angiopathy in contrast to other occlusive processes), T2*, SWI and SWAN (visualization of small hemorrhages) and DWI mode (signs of acute ischemia) are the most advised for MRI [47]. Moreover, contrast-enhanced T1 mode and FLAIR mode are valuable to visualize “ivy sign” caused by typical augmentation of contrast enhancement or hyperintense signal (FLAIR mode) along the fissures and gyri. These changes are associated with slow blood flow through the lep-
assess collateral circulation is still direct selective angiography with separate bilateral contrast enhancement of various arterial pools. According to J. Hendrikse et al., sensitivity and specificity of MR angiography in assessment of collateral circulation are only 33 and 88%, respectively [54].

The main method for cerebrovascular imaging and evaluating collateral circulation is still direct selective angiography with separate bilateral contrast enhancement of ICA, ECA and vertebral artery (VA). This method is recommended in all cases for preoperative diagnosis of moyamoya disease. Direct angiography makes it possible to assess collateral circulation at different levels: basal moyamoya vessels, spontaneous transdural anastomoses from the middle meningeal artery or ECA branches, anastomoses within the circle of Willis, leptomeningeal cortical anastomoses, anastomoses from the ophthalmic artery. Natural collaterals determine the prognosis of disease to a large extent that should be considered in determining the indications for surgical treatment [55, 56]. Analysis of cerebral blood flow (CBF) and grade of cerebrovascular insufficiency is the main factor in planning of treatment strategy in patients with moyamoya disease [57]. The most effective method for measuring cerebral hemodynamics and brain tissue metabolism is positron emission tomography (PET) with an oxygen isotope-15 (15O). However, the widespread use of this approach is limited due to high cost and low availability. Other methods for cerebral blood flow measurement are perfusion CT with bolus contrast enhancement; xenon-enhanced CT (Xe-CT); single-photon emission CT (SPECT); perfusion-weighted dynamic MRI with bolus contrast enhancement and arterial spin labeling MRI (ASL perfusion). Many of these methods are highly sensitive and specific compared to PET, especially in assessment of cerebrovascular reserves: 100 and 83.2% for SPECT [58], 94.4 and 85.2% for CT perfusion [59]. However, most methods are associated with injection of radioactive and contrast agents, irradiation and risk of side effects. This causes significant technical difficulties and limits routine usage of these methods in perfusion survey [60].

Current trends in the development of diagnostic methods are aimed at increasing safety and reducing invasiveness. In this regard, non-contrast ASL MR perfusion has been widely used recently [61]. This technique may be applied at all stages of treatment and in almost all categories of patients. There are advantages of this approach including non-invasiveness, high sensitivity and specificity in assessment of cerebral blood flow (93 and 94% compared to other perfusion methods [62]). However, ASL is also characterized by certain disadvantages, for example frequent arterial transit artifacts (ATA) complicating the quantitative CBF assessment [63]. Further development with modification of this technique (Long label long delay ASL, LLLD ASL) compensated the shortcomings of ASL with standard delay. LLLD ASL perfusion has the highest accuracy in the diagnosis of cerebral blood flow compared to PET (98.5%) [64].

Moreover, the latest modification of ASL perfusion with selective contrast enhancement of different arterial pools by separate arterial spin labeling in different arteries — ECA, ICA, VA (selective ASL) was developed [65]. This innovation opens up the new possibilities for a detailed study of cerebral blood flow in moyamoya disease. An auxiliary diagnostic method for moyamoya disease is electroencephalography. Common EEG phenomenon in children is delayed deceleration (“re-build-up”) as the 2nd phase of high-amplitude slow waves in 20-60 sec after the end of hyperventilation. This sign indicates

### Table 1. Suzuki staging system of moyamoya disease [5]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Narrowing of supraclinoid ICA without moyamoya vessels</td>
</tr>
<tr>
<td>II</td>
<td>Narrowing of supraclinoid ICA and MCA with appearance of moyamoya vessels within subcortical ganglia</td>
</tr>
<tr>
<td>III</td>
<td>Severe stenoses of ICA and MCA with enlarged intracranial collaterals, non-filling of natural extra-intracranial collaterals</td>
</tr>
<tr>
<td>IV</td>
<td>Critical stenoses/occlusions of circle of Willis with intracranial and extra-intracranial collateral networks</td>
</tr>
<tr>
<td>V</td>
<td>Reduction of moyamoya vessels within subcortical nuclei. Enhanced natural extra-intracranial anastomoses</td>
</tr>
<tr>
<td>VI</td>
<td>Occlusion of circle of Willis. Disappearance of intracranial moyamoya vessels. Cerebral blood supply through the extracranial collaterals and cortical anastomoses with PCA pool</td>
</tr>
</tbody>
</table>

Note: ICA — internal carotid artery; PCA — posterior cerebral artery; MCA — middle cerebral artery.
cates decompensated cerebral blood flow. It should be noted that hyperventilation is currently contraindi-
cated in symptomatic patients with a high risk of recurrent stroke, this method is also not recommended for outpa-
tient survey [66].

Considering complex and multicomponent pathogen-
esis of moyamoya disease, diagnostic protocol cannot be
limited by one survey. M. Czabanka et al. analyzed per-
fusion and hemodynamic status with clinical symptoms
and risk of surgical treatment. For this purpose, they pro-
posed a new multimodal classification considering struc-
tural brain changes according to MRI (signs of ischemia/
hemorrhage/atrophy), signs of cerebrovascular insuffi-
ciency (reduced cerebrovascular reserves), as well as di-
rect angiography data on intra- and extracranial collateral
circulation pathways (Berlin Grading System of Moy-
amoya disease) [67]. This classification is valuable to divide
the patients into the risk groups for symptomatic progres-
sion, to identify the most vulnerable groups of patients
and to determine the indications for surgical treatment.

There are large world literature data on the effective-
ness of surgical revascularization in improving clinical
symptoms and reducing the risk of recurrent ischemic
stroke. According to the meta-analysis, revasculariza-
tion was followed by complete disappearance of isch-
emic symptoms in 51.2% of children. Moreover, signif-
cant improvement after any type of surgery was observed
in 35.5% of these patients [68]. In adults, postoperative
stabilization of disease and regression of clinical mani-
festations were noted in 78—81% of cases [69].

Preventive effect of surgical revascularization for re-
current hemorrhages has been previously discussed [42,
70]. An effectiveness of surgical treatment for hemor-
rhagic course of moyamoya disease has been proven in
a large multiple-center randomized Japanese trial (Ja-
pan Adult Moyamoya Trial (JAM), 2014) [71]. Recurrent
hemorrhages were noted in 11.9% of patients after surgi-
cal treatment and in 31.6% of the conservative treatment
group. Subsequently, the positive effect of surgical revas-
cularization for reducing the risk of hemorrhage has been
repeatedly proved in other researches [42, 72, 73]. It was
demonstrated that anastomosis resulted restructuring of
cerebral circulation and involution of “moyamoya” ves-
sels as a possible source of hemorrhage. According to K.
Houkin et al., these changes were observed in 25% of
cases [70]. T. Iwama reported 60% [74]. These data justi-
fied inclusion of surgical revascularization into the offi-
cial guidelines for the treatment of stroke in Japan (class
2, level B) [45] and in the USA (class 1, level B) in 2008
and 2019 [75] as the preferred method for ischemic and
hemorrhagic forms of moyamoya disease.

According to current clinical guidelines, surgical
treatment is advisable in patients with moyamoya disease
grade II—V (J. Suzuki classification) with signs of pro-
gressive cerebrovascular insufficiency and reduced cere-
brovascular reserves. Clinical symptoms, previous hemor-
rhages or their consequences in SWI/SWAN MRI scans
are considered as absolute indications for surgical treat-
ment. Modern treatment strategy of patients with moy-
amoya disease is aimed at reducing the risk of perioper-
ative complications. Therefore, preventive revascular-
ization is recommended even in case of asymptomatic
clinical course with signs of progressive stenosis and im-
paired cerebral perfusion [76].

The purpose of surgical treatment is creating of new
extra-intracranial collaterals for compensation of cerebro-
vascular insufficiency and reducing hemodynamic load-
ning on natural intracranial collaterals.

Surgical treatment of moyamoya disease is distin-
guished by various revascularization procedures based
on pathophysiological features of disease. Each of these
approaches has certain advantages, disadvantages and
limitations. Thus, combination of various techniques
and choosing the optimal surgical strategy are under dis-

cussion.

Table 2. Diagnostic criteria of moyamoya disease according to direct angiography and MR angiography [45]

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Direct angiography</th>
<th>TOF MR angiography (&gt;1.5 T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis or occlusion of the distal segments of ICA and/or proximal segments of ACA and MCA</td>
<td>Moyamoya vessels within the affected arteries</td>
<td>Moyamoya vessels within the affected arteries (two or more signals of “flow voids” in T2/FLAIR MRI within the basal ganglia at least on one side determines the presence of moyamoya vessels)</td>
</tr>
<tr>
<td>Moyamoya vessels within the affected arteries</td>
<td>Bilateral lesion</td>
<td>No underlying disease*</td>
</tr>
</tbody>
</table>

Note. * — explanations in the text. MRI — magnetic resonance imaging.

Surgical treatment of moyamoya disease was first per-
formed in 1970 (extra-intracranial microvascular anas-
tomosis (EICMA) between superficial temporal artery
(STA) and MCA) [77]. This type of surgery was deter-
mined as "direct revascularization". The main advan-
tage of surgery is augmentation of blood flow rate in cor-
tical vessels immediately after suturing the anastomosis.
Some experts suggest double and even triple microvascu-
lar anastomoses to increase blood flow velocity [78, 79].
However, the feasibility of such interventions should be
further studied [80].

The positive clinical effect of direct revascularization
for ischemic form of moyamoya disease has been repeat-

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edly confirmed in multiple studies [81, 82]. A 10-year risk of ischemic stroke is significantly reduced after extra-intracranial bypass surgery. Thus, T. Kim et al. reported stroke in 9.4% and 19.6% of patients following surgery and conservative treatment, respectively [83]. Similar results were obtained by S.B. Lee et al. (16.5% and 66.7%) [84]. According to meta-analysis of J.P. Jeon et al. [82], EICMA not only reduces the risk of ischemic stroke by almost 4 times compared to conservative treatment (OR 0.240, \( p = 0.048 \)), but is also effective for hemorrhagic form of moyamoya disease and reduces the likelihood of recurrent hemorrhage by more than 3 times (OR 0.319, \( p = 0.003 \)).

EICMA is not always technically feasible in patients with moyamoya disease due to severe structural changes of the acceptor and donor arteries and their hypoplasia. Another reason is complex system of collateral circulation through the leptomeningeal arteries that creates hemo-dynamic obstacles for anastomosis functioning [85–87]. This is especially true for young children (up to 5 years old). The number of patent anastomoses is much lower in these patients compared to adults (53% and 94%, respectively) [88].

Another drawback of EICMA is predominant revascularization of MCA system alone due to limited length of the donor branches [89]. This is not enough to replenish circulation in other affected vascular pools (ACA, PCA). For example, M. Teo et al. [90] reported the results of 57 repeated revascularizations. They emphasized patent anastomoses in most cases. However, revascularization of other areas was required. In rare cases, direct revascularization of these areas using long branches of STA or insertion donor vessel is applied. However, such interventions are associated with significant technical difficulties and not always feasible that is evidenced by high incidence of unsatisfactory angiographic outcomes [91, 92]. Thus, EICMA does not ensure revascularization of ACA and PCA in most cases. Therefore, severe lesion of these arteries can determine persistence and progression of clinical symptoms [93].

Alternative surgical approaches for moyamoya disease are various procedures of “indirect” revascularization based on predisposition of these patients to neangiogenesis [88]. The essence of these methods is translocation of well-vascularized soft tissues directly to the brain surface for development of extra-intracranial collaterals (synangiosis) [34]. Similar operations for the treatment of moyamoya disease have been used since the late 70s of the last century [94]. Temporal muscle (J. Karasawa et al. [95]), dura mater (CV Reis et al. [94]) and dissected but not intersected parietal branch of STA combined with inverted dura mater (Y. Matsushima et al. [96]) are used as donor tissues. Various indirect revascularization procedures were proposed later depending on the vascularized tissues (Table 3).

Rare variants of indirect revascularization using pedicled omentum with its cortical transplantation are described in the literature [97]. However, this technique is not widespread due to technical complexity and invasiveness. Current trends imply increased number of sources of collateral circulation and enlarged revascularization area through extended craniotomy. In this regard, combinations of various techniques (encephalo-duro-arterio- myo-synangiosis (EDAMS) and encephalo-duro-arte- rio-synangiosis (EDAS)) are the most widespread among indirect revascularization procedure [98, 99].

Initially, indirect revascularization methods were used mainly if direct anastomosis was impossible [95]. However, favorable clinical and angiographic outcomes, less technical complexity and the possibility of use in almost all patients with moyamoya disease ensured even higher incidence of these surgeries compared to EICMA. Thus, K. Irikura et al. reported restoration of more than 2/3 of MCA pool in 75% of cases and regression of “moyamoya” vessels in 94% of patients after EDAS surgery [100]. Y. Matsushima et al. [96] analyzed 65 patients after EDAS and found TIA regression in 74% of cases within 1 year after surgery and in 97% within 2 years. S.K. Kim et al. [101] reported clinical improvement in 62% of patients after EDAS surgery combined with bilateral frontal EGPS, good angiographic result in 79%, and SPECT perfusion parameters recovery in 70% of cases. T. Kawa- guchi et al. [102] combined multiple trephination holes with EGPS and found signs of neovascularization in 41 (95%) out of 43 trephinations.

Development of new collaterals and achievement of the effect of indirect revascularization require certain time (1—12 months as a rule) [103]. In this case, there is no early postoperative improvement of cerebral circulation. This feature explains the fact that indirect revascularization does not reduce the risk of stroke in early postoperative period in patients with decompensated moyamoya disease and severe cerebrovascular insufficiency. Indirect revascularization methods are also characterized by higher incidence of perioperative complications (up to 7.7% [104] compared to 3.5% for direct surgery [105]).

Combination of direct and indirect methods is also used in order to improve the results of surgical treatment of moyamoya disease. This approach was first described by K. Houkin et al. in 1997 who designated this method as “combined revascularization” [106]. Since that time, this technique has become increasingly used in the treatment of moyamoya disease [107]. Many experts note that an attempt of sewing direct anastomosis should be made in every patient with moyamoya disease for any type of surgery [103]. At the same time, the disadvantages and risk of EICMA can be offset by simultaneous indirect revascularization. This is primarily true for blood flow recovery in those brain areas inaccessible for EICMA.

T. Ishikawa et al. [108] reported high efficiency of combined revascularization for reducing the risk of ischemic lesions, improving intellectual development and overall clinical result. W.S. Cho et al. [109] revealed significant enlargement of the neangiogenesis area after EICMA combined with EDGS both in early (44.2%) and
long-term (54.8%) postoperative period. Moreover, K. Houkin et al. [88] consider indirect revascularization as a backup strategy in case of thrombosis of direct anastomosis. Compared to indirect revascularization (EDAS), combined approach (EICMA with EMS/EDAS) ensures better clinical (74% compared to 56%) and angiographic (74% compared to 44%) results [110].

Currently, all of the above-mentioned brain revascularization methods are used, and the choice of surgical strategy largely depends on surgeon’s opinion and preferences. Nevertheless, combined revascularization is increasingly used in the treatment of moyamoya disease that is reflected in the well-known large samples published in recent years (Table 4) [83, 99, 109, 111–119].

Despite the accumulated experience, development of surgical treatment of moyamoya disease is still far from completion. So, the question of the importance of various factors in the effectiveness of direct and indirect revascularization is still open. It was found that indirect revascularization does not result an extensive network of synangioses in patients with hemorrhagic form of disease [120] in contrast to similar operations in childhood or patients with ischemic form of moyamoya disease [88]. A relationship between the patient’s age and neoangiogenesis was found [88]. The mechanisms of neoangiogenesis remain unknown. Apparently, they are associated with higher activity of growth factors in children than in adults [103]. Adverse factors of neoangiogenesis include atrophic brain changes, ischemic foci, moyamoya syndrome [46]. In such cases, an appropriateness of more complex combined intervention is considered.

Similar questions regarding direct anastomosis arise in younger children and in those with widespread lesion of the entire MCA pool. In such cases, EICMA may not become dominant in brain blood supply. So, S. Amin-Hanjani et al. [121] revealed a decrease in the role of direct anastomosis in cerebral circulation in 6 months after surgery on the background of increased role of synangioses de novo.

A separate problem of surgical treatment of moyamoya disease is prevention of severe perioperative complications, especially in patients with signs of decompensated cerebral circulation. Morbidity rate can reach 16.5% in these patients [112]. Risk factors of complications include local (anastomotic function, cerebral circulation restructuring, cerebral hyperperfusion syndrome) and system-

### Table 3. Indirect revascularization methods

<table>
<thead>
<tr>
<th>Donor tissue</th>
<th>Surgery</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal muscle</td>
<td>Encephalomyosynangiosis</td>
<td>EMS</td>
</tr>
<tr>
<td>Dura mater</td>
<td>Encephalodurosynangiosis</td>
<td>EDS</td>
</tr>
<tr>
<td>Aponeurosis</td>
<td>Encephalodurosynangiosis</td>
<td>EGS</td>
</tr>
<tr>
<td>Aponeurosis + periosteum</td>
<td>Encephalogaleo(periosteal)synangiosis</td>
<td>EGPS</td>
</tr>
<tr>
<td>STA + dura mater</td>
<td>Encephalo-duro-arterio-synangiosis</td>
<td>EDAS</td>
</tr>
<tr>
<td>STA + dura mater + muscle</td>
<td>Encephalo-duro-arterio-my-o-synangiosis</td>
<td>EDAMS</td>
</tr>
</tbody>
</table>

Note. STA — superficial temporal artery.

### Table 4. The largest series of surgical treatment of moyamoya disease reported in recent years

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Patients/hemispheres</th>
<th>Surgery</th>
<th>Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Zhao et al., 2018 [111]</td>
<td>China</td>
<td>500/610</td>
<td>EICMA, EDAS, EICMA + EDAS</td>
<td>4.9</td>
</tr>
<tr>
<td>T. Kim et al., 2016 [83]</td>
<td>Korea</td>
<td>301</td>
<td>EICMA</td>
<td>2.7</td>
</tr>
<tr>
<td>J.J. Liu et al., 2017 [113]</td>
<td>USA</td>
<td>905/1446</td>
<td>EICMA, EDAS, EDAMS, EICMA + EDAS/EDAMS</td>
<td>5.6</td>
</tr>
<tr>
<td>S. Kuroda et al., 2020 [114]</td>
<td>Japan</td>
<td>282</td>
<td>EICMA + EDMAPS</td>
<td>3.2</td>
</tr>
<tr>
<td>W. Shen et al., 2017 [99]</td>
<td>China</td>
<td>4754</td>
<td>EICMA + EDAMS</td>
<td>No data</td>
</tr>
<tr>
<td>G. Acker et al., 2015 [115]</td>
<td>Europe</td>
<td>299</td>
<td>EICMA</td>
<td>No data</td>
</tr>
<tr>
<td>W.S. Cho et al., 2014 [109]</td>
<td>Korea</td>
<td>350</td>
<td>EICMA, EDAS</td>
<td>3.8</td>
</tr>
<tr>
<td>J. Feghali et al., 2019 [116]</td>
<td>Korea</td>
<td>194/241</td>
<td>EICMA, EICMA + EDAMS, EDMAS/EDAS</td>
<td>5.8</td>
</tr>
<tr>
<td>N. Khan et al., 2014 [117]</td>
<td>Europe</td>
<td>86</td>
<td>EICMA, EDAS, EDMAS, EGPS (trephinations)</td>
<td>No data</td>
</tr>
<tr>
<td>Y. Sato et al., 2019 [118]</td>
<td>Japan</td>
<td>236/358</td>
<td>EICMA, EICMA + EDAMS</td>
<td>5.08</td>
</tr>
<tr>
<td>J. Gaillard et al., 2017 [119]</td>
<td>USA</td>
<td>537</td>
<td>EICMA, EDAS</td>
<td>4.5</td>
</tr>
<tr>
<td>Burdenko Neurosurgery Center*</td>
<td>Russia</td>
<td>80/134</td>
<td>EICMA, EDAS/EDMS/EPS, EICMA + EDAS/EDAMS</td>
<td>5.2</td>
</tr>
</tbody>
</table>

ic aspects (first of all, instable systemic hemodynamics triggering ischemic cascade on the unilateral and contra-
lateral side) [122]. Adequate analgesia/sedation is espe-
cially important in children since hyperventilation asso-
ciated with crying can provoke vasospasm and cerebral
circulation impairment. M. Kansha et al. [123] reported
ischemic stroke following unstable intraoperative hemo-
dynamics or inadequate perioperative analgesia in 3.9%
of patients. T. Iwama et al. [124] obtained the highest val-
ues in similar situations (16.9%). Hypoxemia, hypo- and
hypercapnia, hypotension, cerebral vasospasm, hypovo-
lumia, anemia and hyperglycemia should be avoided dur-
ing anesthesia since these conditions can exacerbate isch-
emic damage [123].

Currently, moyamoya disease is considered by ma-
ny experts as the main “natural” clinical model of chron-
ic cerebral ischemia. This fact explains the large num-
ber of clinical, pathophysiological and molecular genetic
studies of this disease. Continuous diagnostic improve-
ments and discoveries in normal and abnormal physiolo-
gy broaden the understanding of this disease. Moreover,
these achievements ensure optimizing treatment strate-
gy despite more than 60-year experience.

Conclusion

Moyamoya disease is characterized by complex
pathogenesis, and surgical methods were confirmed to be
effective in these patients. Various surgical approach-
eds were developed. Combined brain revascularization is
preferred considering an effectiveness of neoangiogene-
sis and indications for EICMA. More comprehensive re-
search of the disease and development of pathogenesis-
based individualized diagnosis and treatment protocols
are required to improve postoperative outcomes and to
prevent severe perioperative complications.

The authors declare no conflicts of interest.

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Commentary

The manuscript is devoted to an urgent problem — epidemiology, diagnosis and treatment of moyamoya disease. This rare disease may be hereditary and is more common in the Asian population. Clinical feature of this disease is a high incidence of ischemic and hemorrhagic strokes and the likelihood of clinical manifestation in childhood and adulthood. Surgical treatment is preferred in patients with moyamoya disease. Effectiveness of this approach is confirmed in various researches. Currently, direct, indirect and combined revascularization is used in the treatment of this disease. The authors of the manuscript are representatives of the leading federal institution of our country and often encounter various rare diseases. They reported a review of modern literature on the diagnosis and treatment of moyamoya disease. The article contains 124 national and foreign references and 4 tables with summarized literature data. The manuscript is written in a good literary language and contains comprehensive and well-grounded up-to-date data on the problem. In general, the article makes a very favorable impression. Undoubtedly, the authors discuss the necessary and interesting issue of diagnosis and treatment of moyamoya disease and report their own experience. The article will be interesting for neurosurgeons, neurologists, vascular surgeons and other specialists.

V.A. Lukyanchikov (Moscow, Russia)
Non-coding RNAs as therapeutic targets in spinal cord injury

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Abstract

Spinal cord injury (SCI) may be followed by persistent motor dysfunction and somatosensory disturbances that negatively influences the quality of life of patients and creates a significant economic burden. Analysis of secondary biological processes associated with changes in genetic expression is becoming increasingly important every day in understanding the pathophysiology of spinal cord injury. The results of international sequencing of the human genome were analyzed in 2004. These data revealed about 20,000 protein-coding genes covering near 2% of the total genomic sequence. The vast majority of gene transcripts are actually characterized as non-coding RNAs (ncRNAs). These RNA clusters do not encode functional proteins and ensure post-transcriptional regulation of gene expression. The clusters may be small (approximately 20 nucleotides) known as miRNAs or the transcripts can enroll over 200 nucleotides defined as long non-coding RNAs (lncRNAs). Some modern studies describe transient expression of microRNA in case of spinal cord injury. These RNAs are associated with inflammation and apoptosis, functional recovery and regeneration. Large-scale genomic analysis has demonstrated the existence of multiple lncRNAs whose expression is associated with some processes of spinal cord injury. IncRNA can be divided into two categories depending on the position in relation to the coding genes: intergenic and intragenic. Intergenic IncRNAs is currently the most studied class. Intragenic IncRNAs can be subdivided depending on the overlap of the coding genes (antisense, intron, etc.). According to recent studies, long non-coding RNAs are abundantly present in the tissues of central nervous system and may be crucial in the pathogenesis of certain diseases of nervous system. At the cellular level, it has been shown that IncRNAs regulate the expression of protein-coding RNAs. Moreover, these molecules are involved into such processes as neuronal death, demyelination and glia activation. This review is devoted to the role of ncRNAs in the pathogenesis of spinal cord injury and their potential use as targets for the treatment of consequences of spinal cord injury.

Keywords: ncRNA, miRNA, lncRNA, spinal cord injury, pathophysiology, glial activation, therapy.

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Abbreviations

SCI — spinal cord injury
ncRNA — non-coding RNA
lncRNA — long non-coding RNA
SC — spinal cord
Traumatic spinal cord injury often results in significant impairment in quality of life and disability. It is associated with impairment and loss of motor and sensory functions, impairment of vital function (respiratory, cardiovascular, gastrointestinal and urinary system dysfunction), musculoskeletal deformities [1, 2]. Annual incidence of spinal cord injury worldwide is 10.5 cases per 100,000 (about 750,000 cases annually). Mean age of victims is 39.8 years. SCI incidence in men is 3.37 times higher than in women. Thus, the most active group of population is under risk that makes important the development of new approaches to the diagnosis and treatment of this lesion [2].

There are two main mechanisms of SCI: primary mechanical and secondary one including inflammation, acidosis, apoptosis and glial scar. The last one is a physical and molecular barrier preventing axonal regeneration [3–5]. Secondary SCI includes astrogliosis as significant augmentation of the number of astrocytes in the area of neuronal injury, infection, stroke or neurodegenerative disease. However, astrogliosis is essential in regeneration processes since it restores homeostasis after SCI, facilitates recovery of blood-brain barrier and suppresses inflammation [6, 7]. Favorable effect of astrogliosis was found in early hypertrophic phase after SCI while development of dense scar in late hyperplastic phase impairs axonal regeneration [8, 9]. In addition to neurons, other SC cells, such as oligodendrocytes and microglia cells are subject to apoptosis [6]. Loss of oligodendrocytes in white matter continues throughout several weeks after SCI and can contribute to progressive demyelination [10, 11].

Changes in gene expression are important in pathogenesis of secondary SCI. However, the mechanisms regulating expression of these genes are unclear. About 70–80% of human genome are actively transcribed in RNAs, while only 2% are transcribed in protein-coding microRNAs. Thus, the number of non-coding RNAs (ncRNAs) is much higher than the number of protein-coding genes. Non-coding RNAs are grouped into two main classes depending on transcript dimension: small and long. Small ncRNAs include well-described microRNAs, small interfering RNAs (miRNAs) and PIWI-interacting RNAs. NcRNAs are good candidates for the role of regulators of secondary SCI since these molecules can ensure post-translational regulation of genes [11–13]. Some forms of microRNAs are essential in embryonic development of nervous system and important mediators of neuronal plasticity [14, 15]. A number of microRNAs have been proved to be involved in the development of severe neurological diseases, such as Tourette's syndrome [16]. Some trials are devoted to the role of microRNAs in neurodegeneration processes [17, 18]. Up to 40% of all known ncRNAs are specifically expressed in the brain and other parts of central nervous system [19]. This finding has shown that long non-coding RNA (IncRNA) can participate in pathogenesis of nervous system diseases. Therefore, identifying the expressed ncRNAs by genomic approaches will be valuable to understand the development of ncRNA-mediated diseases. The role of ncRNA in SCI is still unclear although expression of large amount of ncRNA was found in SC of mice.

**MicroRNA expression in spinal cord injury**

N.K. Liu et al. performed an experiment on rats with traumatic brain injury in order to determine microRNA expression over time [15]. The authors concluded that injured SC in a rat contains approximately 77% (269) of microRNAs identified in a healthy rat (350). Thus, SC is a rich source of microRNA expression. Expression of 97 out of 269 microRNAs changed after SCI. Moderate, high and very high expression of 60 out of 97 microRNAs was found. Expression of other 37 microRNAs was low. SC decompression is preferable surgical treatment of SC trauma. M. Ziu et al. analyzed expression of various microRNAs depending on duration of SC compression [20]. These researchers proved that expression of some microRNAs differs depending on compression time. In particular, miR-107 is expressed in long compression model and does not change in short compression model. Expression of miR-148 is increased in 3 and 6 hours after prolonged compression and after 6 hours in short compression model. It was also shown that miR-210 is expressed after 3, 6 and 24 hours in long compression model and only after 24 hours in short compression model.

**MicroRNA associated with inflammation and apoptosis**

V. Sahni et al. conducted an experiment on mice with SCI and determined the role of bone morphogenetic proteins (BMPs) and their receptors in secondary astrogliosis after SCI [9]. These authors detected significant augmentation of BMP4 in 4, 7 and 15 days after injury. They also found moderate increase of BMP7 levels in 4 days after injury and normalization 7 days later. The researchers also observed increased transcription of 1a BMP receptor (BMPR1a) and GFAP protein (glial fibrillary acidic protein) in 4 and 7 days after injury. BMP signaling pathway includes SMAD proteins (similar to mothers against decapentaplegic). It was shown that these proteins control posttranscriptional processing of miR-21 [17]. The authors analyzed the behavior of this microRNA and demonstrated that BMPR1a-mediated signal transmission inhibits cytoplasmic processing of miR-21. Thus, final processed product of this microRNA is usually inhibited after SCI. O. Bhalala et al. conducted an experiment on mice in order to clarify the role of miR-21 in astrocytic response after SCI [21]. The authors found that miR-21 overexpression in astrocytes after SCI weakens hypertrophic response. Moreover, they observed that miR-21 inhibition is accompanied by increased axonal density at the site of lesion. The authors revealed a new effect of miR-21 in astrocytic regulation of hypertrophy and glial scar progression after SCI. V. Izumi et al. analyzed miR-
MicroRNA associated with functional recovery and regeneration

Regeneration is a reproduction of accurate copies of lost anatomical structures. This phenomenon is observed in some vertebrate species, such as salamanders, axolotls and danio rerio and lost in mammals. Molecular mechanisms of this process are still unclear [24]. The role of microRNA in SC regeneration after injury was studied in some of these species. T. Sehm et al. conducted an experiment on axolotls and determined the role of miR-196 in tail regeneration after its amputation [24]. The authors found significantly increased expression of miR-196 within 14 days after amputation. Inhibition of miR-196 significantly impaired regeneration. These data indicate that this microRNA is essential at the early stages of regeneration of the tail in axolotls. J.F. Díaz Quiroz et al. found that miR-125b is necessary for functional regeneration after SCI in the same species [25]. The authors have shown that reducing the level of miR-125b in axolotl up to that in rats inhibits regeneration through regulation of the Sema4D gene. The last one causes development of glial scar. Y.M. Yu et al. studied the role of miR-133b in functional recovery after SCI [26]. For this purpose, they used a model of SCI in danio rerio and revealed positive regulation of miR-133b in neurons. Inhibition of miR-133b changed motor recovery and reduced axonal regeneration within the spinal cord slice.

Potential targets of microRNA in spinal cord injury

Inflammation, acidosis and apoptosis

N.K. Liu et al. studied the role of microRNA after SCI in analysis of potential target genes [15]. Statistical analysis demonstrated that these targets are genes encoding the components involved in various physiological processes such as inflammation, acidosis and apoptosis. Genes inhibiting inflammatory process are potential targets for some microRNAs (miR-221, miR-1, miR-206, miR-152, miR-122, miR-181a, miR-411, miR-99a, miR-34a, miR-30c, miR-384-5p, miR-30b-5p and miR-214). A number of genes responsible for apoptosis are potential targets for microRNA. Expression of these microRNAs is reduced after SCI (miR-127, iR-181a, miR-411, miR-34a and miR-384-5p). According to available data, abnormal expression of microRNA after traumatic SCI is essential in secondary damage of the spinal cord. Thus, these microRNAs may be potential targets in SCI management. V. Sahni et al. reported that miR-21 negatively regulates reactive hypertrophy of astrocytes in SCI [9]. However, the authors have not yet been able to identify the targets of miR-21, which can affect astrocyte size enlargement. G.Liu et al. studied microRNA associated with apoptosis and showed that increased expression of Let-7a was accompanied by increased expression of RAS (genes and proteins (so-called small G-proteins (small GTPases))) and MYC (genes regulating cellular proliferation, differentiation and carcinogenesis) in 10 days after lesion. However, expression of RAS and MYC normalized after 31 days although Let-7a level remained elevated [23]. On the one hand, increased expression of microRNA was due to increased expression of Bcl-2. On the other hand, exercise after SCI was shown to be maintaining muscle mass in paralyzed limbs, stimulating anatomical and biochemical plasticity in spinal cord and increasing the level of neurotrophic factors in muscles and spinal cord [27—32]. These data justified a research of the effect of physical exercise on expression of some microRNAs [23]. In this trial, G. Liu et al. showed that exercise within 5 days after SCI was accompanied by significantly increased expression of miR-21 with anti-apoptotic effect and reduced expression of miR-15b [23]. Increased expression of miR-21 resulted decrease in expression of RNA-messenger PTEN (phosphatase and tensin homolog) and PDC4 (programmed cell death protein 4). Inhibition of these proteins is known to be associated with reduced apoptosis in cancer cells through inhibiting protein kinases B [23].

Functiona recovery and regeneration

T. Sehm et al. studied potential targets of miR-196 for tail regeneration in axolotl [24]. The authors confirmed that this microRNA directly influences the Pax7 gene and suppresses the levels of the expressed protein. Thus, this microRNA affects cell division during regeneration and produces a small tail phenotype. This protein produced the phenotype through a feedback loop with BMP4 and Msx1 (Msh homeobox 1) proteins. These proteins are necessary to control cellular proliferation in the spinal cord. As soon as miR-125 was determined as an important factor for regeneration, J.F. Díaz Quiroz et al. analyzed the effect of increased level of miR-125b in rats after SCI [25]. They injected a synthetic variant of miR-125b into the lesion site in 7 days after injury and showed reduced level of Sema4D, development of the glial scars and positive effect on functional recovery (improved movement in some animals). Y.M. Yu et al. analyzed the role of miR-133b in functional recovery after SCI. They found that this microRNA is important for SC regeneration in danio rerio. Regeneration is associated with reduced level of RhoA protein (RAS homolog gene family, member A) of small GTPase (guanosine triphosphate) [26]. The regularities of activation of this protein after SCI and its role in apoptosis of CNS cells have been studied [33]. Both proteins originating from myelin and
tumor necrosis factor directly activate Rho. Inactivation of Rho C3-05 (RAS homolog gene family, member C3-05, antagonist of RhoA) after SCI blocks augmentation of p75NTR protein (p75 neurotrophin receptor) and inhibits apoptosis. Rho C3-05 inactivation prevents apoptosis and stimulates regeneration. MiR-133b causes this reduction through direct interaction with RNA mediator RhoA. This is an important conclusion, since it was shown that inactivation of this GTPase leads to restoration of coordination between anterior and posterior limbs in mice [34].

Functional role of IncRNA in spinal cord injury

Recently, new characteristics of differentially expressed lncRNAs have been discovered in SCI. In particular, IncRNA-mediated modulation of glial activation and neuronal apoptosis has become an area of intensive research.

Glial activation

Glia may be activated within 1 day (microglia activation) and persist for months or even years (astrogliosis) after SCI [35—37]. In the model of acute blunt SCI in rats, it was found that the level of MALAT1 protein (metastasis associated lung adenocarcinoma transcript 1) is significantly increased within the damaged area of SC [38]. MALAT1 activates miR-199b and contributes to release of proinflammatory cytokines. Inhibition of spinal MALAT1 led to decrease in expression of microglial marker Iba-1 and proinflammatory cytokines in the epicenter of contusion and improvement of motor function of posterior limb. However, the role of MALAT1 in microglial polarization has not been studied in this research. Other authors found that expression of ncRNA IncSCIR1 is continuously decreased in 1, 4 and 7 days after moderate blunt SCI [39]. The amount of IncSCIR1 inversely correlated with expression of bone morphogenetic protein 7 (Bmp7) and adrenomedullin (Adm). These proteins contribute to spinal cord astrogliosis [40, 41]. Inhibition of IncSCIR1 stimulated migration and proliferation of cultivated astrocytes [39]. However, most functional studies were performed in vitro. Nevertheless, these studies ensured preliminary evidence that IncRNA can participate in gliogenesis after SCI.

Neuronal apoptosis

Neuronal death is the most obvious consequence of spinal cord injury, especially in acute phase of lesion. Therefore, the molecules-modulators of neuronal apoptosis constantly attract the attention of researchers. XIST (X-inactive specific transcript) was identified as one of the active IncRNAs with the greatest multiplicity of changes in the number of molecules in the model of SC contusion in mice [42]. Inhibition of XIST had a significant neuroprotective effect through activation of (PI3K)/AKT protein in damaged SC. Inhibition of XIST was followed by increased expression of miR-494. Then, the last one inhibited PTEN deletion. Reducing PTEN activated PI3K/AKT pathway and protected neurons from apoptosis.

Possible therapeutic approaches

The role of microRNA in SCI needs further study. However, there are multiple data on microRNAs as a new class of therapeutic targets [43—45]. MicroRNAs reduce protein levels in central nervous system through posttranscriptional regulation [16, 46]. Thus, inhibition of microRNA associated with a specific disease can eliminate the blockade of expression of the desired protein. On the contrary, introduction of microRNA mimetics can stimulate endogenous microRNA suppressing the desired gene [47]. Some modified RNAs may be used as pre-microRNA or as oligonucleotides against microRNA [48]. Oligonucleotides against microRNA are complementary nucleotides with reverse chain. Their stability and specificity are improved by chemical modifications. It was shown that oligonucleotides with 2’-O-methyl-modification are effective inhibitors of several cell lines and cultured neurons [49—51]. MicroRNAs mimic small, usually double-chained, chemically modified oligonucleotides which can be used to inhibit specific target proteins. The double-chained structure is necessary for effective association with RISC (RNA-induced silencing complex). One of the chains is a mature microRNA, and the complementary chain forms a complex with a sequence of mature microRNA [51]. There is still no evidence of efficacy of these simulators although they are often used in crop studies [52]. There are still many challenges to use microRNAs as therapeutic targets including difficult introduction, possible effects on other genetic systems and ensuring safety. However, the strategy of manipulating microRNA in vivo for regulation of abnormal processes is becoming possible as a therapeutic approach. A better understanding of their biosynthesis and function will undoubtedly facilitate the development of microRNA therapy.

Conclusion

Spinal cord injury is a cause of disability in working-age population. This serious clinical problem is still requiring intensive research. Non-coding RNAs are also analyzed in this pathology. As a result, their importance in control of inflammation, acidosis, apoptosis, proliferation and regeneration was emphasized. Further studies of non-coding RNAs in spinal cord injury, identification of target genes and signal transmission pathways are needed. Non-coding RNAs participate in various cellular and tissue changes at all stages of spinal cord injury through interaction with a network of coding genes. Thus, deregulation of non-coding RNAs is a new approach to influence on molecular mechanisms in spinal cord injur-
ry. The ultimate aim is to develop an effective and safe therapeutic and diagnostic strategies for patients with spinal cord injury.

Authors’ participation:
Concept and design of the study — O.B., N.K.
Collection and analysis of data — Sh.A., A.A., A.B.

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Analysis of data — Sh.A., A.A., A.B.
Writing the text — I.G.
Editing — O.B., N.K.

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Cysts of septum pellucidum, cavum vergae and cavum veli interpositi. Meta-analysis of 368 cases

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Abstract

Objective. To review and systematize literature data on the incidence of cysts of septum pellucidum, cavum vergae and cavum veli interpositi, their clinical manifestations, indications for surgical treatment and optimal surgical approach.

Material and methods. An analysis included 72 manuscripts devoted to epidemiology, pathophysiology, clinical symptoms and results of surgical treatment of brain cysts. Case reports, series of cases, reviews and original studies were analyzed.

Results. Septum pellucidum cavity is always formed throughout an embryogenesis and persists in 20.34% of adults. Cavum vergae is observed in 2.32% of adults. Cyst of septum pellucidum is detected in 0.04% of adults. Analysis of 368 cases of cysts of septum pellucidum, cavum vergae and cavum veli interpositi has shown that clinical picture consists of headache (50% of cases), convulsive syndrome (23.6%), reduced intelligence (20.1%), behavioural disorders (15.8%), dizziness, nausea and vomiting (10.9%). Hydrocephalus occurs in 16.6% of cases. Endoscopic wall fenestration is preferred for cyst management.

Conclusion. Brain cysts are rare and characterized by non-specific clinical manifestations. Symptomatic cyst is an indication for surgical treatment. Surgical treatment usually ensures regression of symptoms and low risk of complications.

Keywords: cyst of septum pellucidum, brain cyst, cavum vergae, cavum veli interpositi, hydrocephalus, malformations, endoscopic fenestration.

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Abbreviations

SPC — septum pellucidum cyst
CVC — cavum vergae cyst
CVIC — cavum veli interpositi cyst
CT — computed tomography
MRI — magnetic resonance imaging
CV — cavum vergae
SP — septum pellucidum
CVI — cavum velum interpositum
Cysts of septum pellucidum (SPC), cavum vergae (CVC) and cavum veli interpositi (CVIC) are the most common among CSF cysts of median localization.

The purpose of the study was to review and systematize literature data to the incidence of SPC, CVC and CVIC, their clinical manifestations, indications for surgical treatment and selection of optimal surgical approach.

Material and methods

Searching for literature data was carried out in the PubMed, Google Scholar and Cochrane Library databases using the following keywords: septum pellucidum cyst, cavum vergae cyst, cavum veli interpositi cyst, endoscopic fenestration, hydrocephalus. Original articles, reviews and case reports were selected. We did not include non-Russian and non-English language manuscripts, as well as those with unavailable abstract and full text. Reports on asymptomatic cysts were also excluded from the analysis. The data obtained were grouped and analyzed using Microsoft Excel software package. Incidence of the following symptoms was determined: headache, optic nerve swelling; cranial nerve dysfunction (any type); convulsive syndrome; impaired intelligence and delayed psychomotor development (in children); dizziness, nausea, and vomiting; gait disturbance; visual impairment (any type); mental disorders (agression, hyperactivity, apathy, abulia, depression, etc.); hydrocephalus. We have analyzed literature data on the mechanisms, structure, epidemiology and pathophysiology of these cysts, their classification, diagnosis, indications for surgery and methods of surgical treatment. Analysis of clinical manifestations did not imply distinction between asymptomatic cysts of septum pellucidum, cavum vergae and cavum veli interpositi.

Results

There were 123 reports in accordance with searching criteria (available abstract or full text — 72 studies). The vast majority of manuscripts (57.79%) were case reports and descriptions of small series (<5 cases); samples over 5 patients were described in 15 (21%) manuscripts, samples over 10 patients — 8 (11%) publications. Literature data on the incidence of certain clinical manifestations and hydrocephalus in patients with symptomatic cysts are summarized in Table 1. Data on the incidence of SPC, CVC and CVIC are shown in Table 2 [1—11].

Discussion

Cavum vergae was described by Jacques Dubois (Silvius) in 1671 [12]. The first reliable evidence on a cavity between anterior pillars ("ventriculus fornicus seu cavum Vergae") was presented by the Italian neurologist and psychiatrist Andrea Verga in 1851 [13]. It is noteworthy that brain specimen was harvested from a patient who died from hydrocephalus. W.E. Dandy first described surgical treatment of a patient with SPC in 1931 [14].

Anatomical features of the areas with possible development of cysts are shown in Fig. 1. It should be noted that it is customary to distinguish the concepts of cavities and cysts [16]. SPC, CVC and CVIC are characterized by fluid accumulation with a thickness of more than 10 mm and wall protrusion towards the lateral ventricles [17—21]. Currently, these findings are clearly visualized during computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 2). It was also shown that CVI and CV are not a part of brain ventricular system and have no ependymal. These structures are characterized by another embryogenesis and normally do not communicate with the ventricles [22].

Epidemiology. CVI is detected in a fetus up to 8.5 months of gestation in 100% of cases. CV occurs in 60% of children of the first year of life and in 30% of children aged 1 — 10 years and usually does not cause clinical symptoms. In adults, CVI is observed in 20% of cases, CV — 2%. Cysts occur in 0.04% of cases. Large SPC and CVC may be combined with other congenital anomalies of central nervous system: agenesis of the corpus callosum, optic nerve hypoplasia, cortical atrophy, encephalo- and meningomyelocele, etc. [23, 24]. A higher incidence of SPC and CVC was noted in patients with schizophrenia and other mental illnesses [12, 24, 25], as well as in boxers [26].

Classification. W.P. vanWagenen et al. identified 3 types of SPC [1]:

1. Non-communicating — a cavity is isolated from other CSF spaces.
2. Communicating — cavity communicates with the lateral ventricles due to rupture of one or more cystic walls.
3. Secondary (or acquired) — there is enlargement of cavum septi pellucidi communicating with the lateral ventricles due to hydrocephalus (Fig. 3) [27].

Pathological physiology. Numerous histological studies of cystic walls did not reveal ependymal cells or choroid plexus for cerebrospinal fluid release [28]. A possible mechanism of cyst enlargement is cerebrospinal fluid transudation from the lateral ventricles [29]. CSF release into the cyst may be carried out by residual embryonic cells of arachnoid membrane localized in cystic walls. However, this assumption is not histologically confirmed [30]. Assumptions on migration of cells capable for CSF release to cavum septi pellucidi [31], or transformation of cystic wall cells into those capable for CSF release [32] were made. These processes result transformation of cavum septi pellucidi to SPC. In this case, there are cyst enlargement, compression of local structures (limbic system, motor tracts, optic tracts) and veins, spontaneous rupture of a cyst with clinical regression, formation of a “scar” in the wall and true
Table 1. Incidence of various symptoms and hydrocephalus in patients with symptomatic midline cysts

<table>
<thead>
<tr>
<th>Symptom, n (%)</th>
<th>Number of reports</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Headache</td>
<td>184 (50)</td>
<td>368</td>
</tr>
<tr>
<td>Convulsive syndrome</td>
<td>87 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Reduced intelligence/delayed psychomotor development</td>
<td>74 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Mental disorders</td>
<td>58 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Dizziness, nausea, vomiting</td>
<td>40 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>36 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Gait disorders</td>
<td>33 (9)</td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
<td>31 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Optic nerve swelling</td>
<td>17 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve dysfunction</td>
<td>15 (4)</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>61 (16.6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Epidemiology of midline brain cysts

<table>
<thead>
<tr>
<th>Manuscript</th>
<th>Methods</th>
<th>Number of cases</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.P. van Wagenen, 1934 [1]</td>
<td>Autopsy of non-fixed specimens</td>
<td>30</td>
<td>Unknown</td>
<td>SPC — 60%</td>
</tr>
<tr>
<td>J.T. Schwidde, 1952 [2]</td>
<td>Autopsy of fixed specimens (10% formaldehyde solution)</td>
<td>1032</td>
<td>Newborns, children, adults aged up to 90 years</td>
<td>CSP — 20.34% CV — 2.32%</td>
</tr>
<tr>
<td>Larroche J.C. et al. 1961 [3]</td>
<td>Autopsy</td>
<td>No data</td>
<td>No data</td>
<td>CSP — 100% &lt;8.5 months, 82% full-term infants CV — 100% &lt;6 months, 30% full-term infants</td>
</tr>
<tr>
<td>H. Schunk 1963 [4]</td>
<td>Images of macroscopic specimens</td>
<td>307</td>
<td>Patients died of neurological diseases</td>
<td>CSP — 60.2% CSP &gt; 5 mm — 0.9%</td>
</tr>
<tr>
<td>Nakano S. et al., 1981 [7]</td>
<td>CT</td>
<td>1050</td>
<td>Newborns and children aged under 14 years with neurological diseases</td>
<td>CSP — 2.2% CSP+CV — 3% CV — 0.4%</td>
</tr>
<tr>
<td>K. Akiyama et al., 1983 [8]</td>
<td>CT</td>
<td>2722</td>
<td>Adults</td>
<td>CSP — 2.6%</td>
</tr>
<tr>
<td>S.H. Mott et al., 1992 [9]</td>
<td>Transcranial ultrasound</td>
<td>108</td>
<td>Premature infants (&lt;35 weeks)</td>
<td>CSP — 100% mean cavity width — 5 mm</td>
</tr>
<tr>
<td>J. Kwon et al., 1998 [10]</td>
<td>MRI</td>
<td>113</td>
<td>Patients with mental disorders and control group</td>
<td>CSP &gt; 5 mm — 30.4% of patients with schizophrenia and 10.3% in the control group</td>
</tr>
<tr>
<td>K. Wang et al., 2004 [11]</td>
<td>CT and MRI</td>
<td>54000</td>
<td>Unknown</td>
<td>SPC — 0.04%</td>
</tr>
</tbody>
</table>

Note. SPC — septum pellucidum cyst; CT — computed tomography; MRI — magnetic resonance imaging; CV — cavum vergae; CSP — cavum septi pellucidi.

cyst [31]. Cyst enlargement is accompanied by impaired venous outflow [29]. A risk factor of transformation of cavum septi pellucidi into SPC is a “chronic” traumatic brain injury. Frequent SPC has been described in professional boxers [26]. There is also suggestion on a valve mechanism of CSF accumulation in the cyst [21, 33].

Clinical manifestations. Symptoms of SPC often form the so-called “SPC syndrome” [34]: a combination of impaired behavior, ataxia, speech impairment, seizures, and bilateral pathological plantar reflexes. Headache is characterized by postural nature [35] and aggravation after Valsalva test. SPC and CVC do not cause occlusive hydrocephalus and clinical manifestations per se. However, these cysts can complicate the course of other
diseases, for example, cause occlusive hydrocephalus in patients with brain tumors [36]. SPCs complicate endoscopic and bypass surgery, external ventricular drainage [37]. Amnestic syndrome was described in a patient with SPC. Cystic wall perforation was followed by regression of symptoms [38].

Additional survey methods. CT cisternography is the most informative method for the diagnosis of midline cavities and cysts. It is possible to evaluate in detail the presence or absence of communication between brain ventricular system and these additional cavities and cysts considering features of contrast enhancement CSF-containing cavities. Surgery is indicated for intracerebral occlusion of CSF circulation. MRI is less informative as an alternative method for examination of CSF circulation. This method ensures imaging of cerebrospinal fluid flow at the level of Sylvian aqueduct, third ventricle. However, analysis of communication of additional cerebrospinal cavities with ventricular system is impossible.

Surgery. Microsurgical cystoventriculostomy, cystoperitoneal bypass and stereotactic puncture and drainage of midline cerebrospinal fluid cysts are currently extremely rare. These procedures cause brain matter injury (microsurgical cystoventriculostomy) that is incompatible with clinical manifestations. Moreover, these techniques are ineffective due to small dimension of a stoma (stereotactic puncture and drainage of midline cerebrospinal fluid cysts). It was found that endoscopic fenestration is the most optimal approach [39]. Single and bilateral approaches, occipital and frontal approaches, flexible or rigid endoscope and the need for external ventricular drainage are still debatable [40–44] (Fig. 4).

**Conclusion**

Cysts of septum pellucidum, cavum vergae and cavum veli interpositi are very rare. These cysts can cause various non-specific cerebral and local neurological symptoms. MRI and CT may be used to identify and estimate dimensions of cysts. However, more accurate methods of dynamic imaging with assessment of cerebrospinal fluid circulation are needed for comprehensive analysis. Surgical treatment of midline cerebrospinal fluid cysts is indicated for isolated cavity (CT cisternography data) combined with clinical symptoms, which cannot be explained by any other diseases characterized by similar clinical picture.

**Authors’ participation:**
Concept and design of the study — E.K., Sh.G.
Collection and analysis of data — A.S., Sh.G., G.G.
Writing the text — A.S., G.G.
Editing — E.K.

The authors declare no conflicts of interest.
Fig. 2. Differential diagnosis of midline cavities and cysts according to MRI data.
Explanations in the text.

Fig. 3. Classification of CSP depending on dimensions (MR scanning in coronal plane) [27].
CSP is measured with the following grading from 0 (no visible cavity) to 4 (SPC with narrowing of lateral ventricles).

Fig. 4. Variants of neuronavigation-assisted endoscopic fenestration of SPC [44].
a — entrance into the cyst is performed after ventriculostomy of the lateral horn (arrow); b — direct puncture of SPC (big arrow).
REFERENCES

A review is devoted to midline cerebrospinal fluid cysts, examination and treatment of cystic enlargement of cavum septi pellucidi, cavum vergae and cavum veli interpositi.

Cavum vergae is a continuation of interventricular septum cavity into the space under corpus callosum between fornix columns. At the same time, cavum veli interpositi is characterized by another histogenesis. It is a triangular fissure between two laminae of pia mater of the third ventricle roof. This cavity is localized above a hippocampal commissure and internal brain veins and faces towards interventricular orifices. Cavum veli interpositi is initially associated with a cistern of corpora quadrigemina. This cavity is being emptied in prenatal period and becomes indistinguishable in most full-term infants. Persistence of this cavity in few cases has no clinical significance.

Septum pellucidum develops at the 12th week of gestation from embryonic commissural (terminal) lamina. The last one is invaginated between the fornixcolumns and expands over anterior or commissure in the form of two thinning laminae. This process occurs in rostral direction following genu of corpus callosum, over anterior parts of the third ventricle and anteriorly from these structures. A fissure following these processes is being closed gradually along with development of the forebrain and subcortical nuclei. However, this process is not early, and fissure persists until late adolescence in some cases (adulthood in rare cases). Residual fissure is not associated with mental diseases or other disorders accompanied by delay in mental and speech development, headache, intracranial hypertension and optic nerve swelling [1].

The authors rightly emphasize an importance of differences between persistence of these cavities as a normal brain development and maturation and their cystic enlargement. For this purpose, large literature data on morphology, CT and MRI signs, incidence of these cysts and various clinical manifestations (with predominant headache) are analyzed. Other syndromes including epilepsy, mental disorders and delayed psychomotor development can hardly be considered indication for neurosurgical examination and treatment even if these disorders are related to the cysts.

What features turn these generally indolent cavities into clinically significant cysts? These cysts contain cerebrospinal fluid. In any case, neither me, nor, as far as I know, anyone else saw anything else there. I can’t say for sure where CSF comes from. Although various authors often talk about CSF transudation through the walls into the cavity, it seems to me (and other researchers [2]) that searching for communication in the area of primary development of this cavity is more logical. This is a tiny triangular space between fornixcolumns and anterior commissure within anterosuperior walls of the third ventricle. In some cases, early obliteration of fissure precedes occlusion of cavum septi pellucidi. Thus, a cyst of septum pellucidum occurs in the full sense of the word. Apparently, this process is caused by various events (trauma, infection). Oscillating pressure gradient delivered to brain ventricle walls by a pulse wave from the brain base major arteries is not coincided with cerebrospinal fluid pulse in the cyst if the cavity is spacious by this time. Phase and direction of these waves are different. Thus, a phenomenon of a “water hammer” along the hypothalamic structures (in front) and deep brain veins (posteriorly and from below) explains the symptoms in our patients (persistent headache, depression, anorexia, lethargy, impaired memory, etc.). Immediate regression of these symptoms after restoration of communication between the ventricles and the cyst is its obvious confirmation.

Importantly, a volume of supratentorial cerebrospinal fluid spaces including lateral ventricles and cysts themselves in patients with cysts of septum pellucidum and cavum vergae does not usually exceed that in people of the same age and brain volume [1]. “Taking away” this volume from the ventricles, on the one hand, affects cerebral blood flow autoregulation, which is closely related to cerebrospinal fluid circulation. On the other hand, the cysts increase an amplitude of intracranial pressure oscillations for compensatory acceleration of cerebrospinal fluid flow velocity due to stenoses of interventricular orifices. Both aspects together cause a persistent headache and brain ventricle enlargement after depletion of brain tissue elasticity reserves.

The authors briefly indicate that such cysts “...complicate neurosurgical interventions”. I do not agree with this statement. Fenestration of their walls, on the contrary, only improves visualization and intraventricular manipulations. In other situations, for example, interfornical approach to the third ventricle, cavum septi pellucidi is a very convenient and reliable landmark.

Only surgical treatment is advisable for symptomatic cysts. Endoscopic cystoventriculostomy is preferred. However, stereotactic navigation is highly desirable, especially in patients with narrow ventricles. Risk of severe complications is very high without such support

A.G. Melikyan (Moscow, Russia)

REFERENCES
