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Topics to be covered in our next issue

- Intraoperative mapping of long associative tracts in surgery for tumors of language-dominant frontal lobe
- Extended transsphenoidal surgery for suprasellar meningiomas
- Liquorrhea after resection of tumors of the fourth ventricle in children
Clinical course of the disease as well as anatomical and morphological features of aneurysms are the main criteria determining the choice of surgical treatment in patients with aneurysms of intracranial segments of the cerebral arteries.

The main types of clinical manifestations of cerebral aneurysms are listed below:

— asymptomatic (not bleeding, incidental finding) aneurysms;
— not bleeding symptomatic aneurysms;
— aneurysms in the acute period after spontaneous intracranial hemorrhages;
— aneurysms in the cold period after spontaneous intracranial hemorrhages.

The term “anatomical and morphological characteristics of an aneurysm” included its location, size, configuration, condition of its walls, and presence of thrombi in its cavity. In this case, we are talking about aneurysms localized in the intradural segments of the cerebral arteries, as opposed to aneurysms at the level of the cavernous segment of the carotid artery or brachiocephalic arteries.

All of the above criteria are general, they apply to all patients with cerebral aneurysm and fully characterize an aneurysm and clinical situation.

We developed the algorithms for selecting the tactics and methods of surgical treatment of patients with this pathology based on these criteria, rather than considering individual criteria, such as patient’s age, somatic status, presence and nature of concomitant diseases, including stenosing atherosclerotic diseases of the brachiocephalic arteries, conditions requiring constant antiplatelet therapy, etc. These individual criteria are very important for a particular patient, they can be used to adjust surgical treatment, but there are a lot of these criteria and they do not apply equally to all patients with aneurysms and, therefore, cannot be generalized. For this reason, they are not reflected in the proposed algorithms.

Earlier, we published the article focusing on the algorithms of surgical treatment of patients with cerebral aneurysms in the acute period after spontaneous intracranial hemorrhages [1], and therefore we will not cover this topic in the present article. Furthermore, this study does not cover cases of not ruptured but symptomatic cerebral aneurysms. These aneurysms are in most cases giant, often with a thrombosed cavity and sclerotic walls, and present with a clinical picture of mass effect on the adjacent structures of the brain (pseudotumoric course) or symptomatic thromboembolism of the main arteries in the form of transient cerebral circulation disorders or ischemic stroke. These aneurysms require an individual approach and non-standard decisions regarding the choice of the method of surgical treatment. This publication is aimed at substantiating the choice of the method or combination of several methods of surgical treatment of patients with asymptomatic cerebral aneurysms and cerebral aneurysms in the cold period after spontaneous intracranial hemorrhage. Despite the principal differences in the clinical manifestation of these aneurysms, there are many common approaches when choosing methods for their surgical treatment.

Based on the results of microsurgical and endovascular operations for aneurysms in the cold period after spontaneous intracranial hemorrhages and in patients with asymptomatic cerebral aneurysms, we determined the main guiding criteria used to select the method of surgical treatment of patients with this pathology.

In the case of unruptured asymptomatic aneurysms (UAA), the possibility of endovascular intervention is considered as the first option. In this situation, psychological factor plays a significant role. Patients with asymptomatic aneurysms do not feel sick, they have no idea of intracranial hemorrhage and associated life threatening condition and are psychologically not ready for an intracranial operation, which is solely aimed at preventing possible intracranial hemorrhage. Therefore, minimally invasive endovascular operation seems to be the most acceptable solution of this problem. Indeed, the use of flow diverting stents (FDS) and stent-assisted aneurysm occlusion with micro-coils significantly improved the possibilities.
of endovascular surgery to exclude large and giant aneurysms with wide necks, which could not be previously treated using endovascular surgery. FDSs should not be used to treat aneurysms within the first 3 months after hemorrhage due to the risk of recurrent hemorrhage. In this point, we agree with the literature data [2—4]. There is no fundamental difference in the choice of surgical treatment in patients with UAA and aneurysms 3 months after spontaneous subarachnoid hemorrhage (SAH). Of course, we are talking only about general criteria and not about individual ones, as was said earlier. As for the aneurysms within 3 months after SAH, they were treated in the same manner as aneurysms in the acute period of SAH in terms of choosing the method of endovascular exclusion.

The basic principles of selecting surgical treatment in patients with UAAs and aneurysms in the cold period after spontaneous SAHs are listed below (Fig. 1).

1. Small and medium-sized aneurysms of the ophthalmic segment of the ICA are subject to occlusion with micro-coils. Large and giant aneurysms located at this site (when FDS cannot be used) are preferably excluded by microsurgical clipping using the intravascular blood aspiration from the aneurysm. This risk is also present in the case of microsurgical clipping of these aneurysms, but it is more common with the medial location of the aneurysmal sac due to the need for aneurysm dissection and separation of the sac from the optic nerve.

This risk is also present in the case of microsurgical clipping of these aneurysms, but it is more common with the medial location of the aneurysmal sac due to the need for aneurysm dissection and separation of the sac from the optic nerve. After aneurysm clipping, it is usually advisable to open the sac in order to control complete aneurysm exclusion from the blood flow, which simultaneously plays a role of optic nerve decompression. FDS insertion results in gradual aneurysm thrombosis and retraction of blood clots in the aneurysm is possible in the future, which also reduces optic nerve compression and improves vision.

1. Aneurysms of the supraclinoid segment of the ICA (at the segment of the posterior communicating artery) are subject to occlusion with micro-coils, while more distal aneurysms located in the region of the anterior ciliary artery at the bifurcation of the internal carotid artery, where there is a risk of occlusion of the anterior ciliary artery or small perforating arteries are usually subject to clipping. At the same time, this does not rule out the use of the endovascular techniques.

2. Aneurysms of the middle cerebral and anterior communicating arteries are usually excluded from the bloodstream using microsurgical technique. Endovascular interventions should be considered only in exceptional cases, which, as a rule, may be associated with individual criteria. Endovascular interventions aimed at occlusion of aneurysms located at this site together with the artery are also considered in very rare cases, when direct surgical intervention cannot be performed for any reasons.

3. All aneurysms of the trunk and bifurcation of the basilar artery, as well as aneurysms of the posterior cerebral artery, are subject to endovasal exclusion (aneurysm occlusion with coils either with or without stent assistance, or the use of FDS). Microsurgical clipping of aneurysms at this position is considered only in exceptional cases, when endovascular intervention is impossible for any individual criteria.

4. It is advisable to use microsurgical clipping to exclude aneurysms of the vertebral artery located at the mouth of posterior inferior cerebellar artery (PICA) and peripheral aneurysms...
of the PICA and endovascular technique for other aneurysms of
the intracranial portion of the vertebral artery located distal to
the PICA mouth.

5. Distal aneurysms of the anterior, middle, and posterior
cerebral arteries are mostly subject to microsurgical clipping
(except for cases when direct surgical intervention is impossible
for any individual limitations) or the aneurysm is excluded to-
together with the artery.

Selection of the method of surgical treatment, order and
combination of microsurgical and endovascular treatments of pa-
tients with multiple cerebral aneurysms in the cold period after
spontaneous intracranial hemorrhage and UAA is associated
with certain complications. An anatomical and topographic
classification of multiple cerebral aneurysms adopted at the
Burdenko Neurosurgical Institute is as follows [5, 6].

I. Multiple ipsilateral aneurysms of the anterior segment of
the circle of Willis (aneurysms of one carotid system).

II. Multiple bilateral aneurysms of the anterior segment of
the circle of Willis (aneurysms of two carotid systems).

III. Multiple aneurysms of one carotid system and aneu-
rysms of the vertebrobasilar system.

IV. Multiple aneurysms of two carotid systems and aneu-
rysms of the vertebrobasilar system.

V. Multiple aneurysms within the vertebrobasilar system.

Despite the principal difference in the clinical course of
the disease, these patients are quite similar from a purely surgical
point of view. The main task is to identify the “priority” aneu-
rysm, i.e. the one subject to surgical intervention in the first
place. In a patient with multiple aneurysms in the cold period of
aneurysmal hemorrhage, it is the aneurysm which caused hem-
orrhage. In 99—100% of cases, it can be detected taking into
account focal neurological symptoms and using modern X-ray
diagnostic methods [7, 8]. As a rule, this is the largest aneurysm
in a given patient, often with uneven contours and diverticula.
These aneurysms have the greatest risk of rupture and must be
excluded from the bloodstream in the first place. In all cases,
exclusion of the priority aneurysm from the blood flow using
one or another method is followed by making a decision about
exclusion of maximum possible number of aneurysms within
one surgical intervention. When using microsurgical opera-
tions, it is possible in the case of ipsilateral aneurysms of the
anterior segments of the circle of Willis, which can be clipped
along the primary surgical approach; sometimes it is even pos-
sible in the case of aneurysms located on the opposite side, us-

![Fig. 2. The choice of the method for surgical treatment of patients with multiple asymptomatic aneurysms and multiple aneurysms in the cold period after SAH, options I—II (more than 3 months).](image)

CS — carotid system; EO — endovascular occlusion; ES — endovascular stenting; MC — microsurgical clipping.
The Burdenko Neurosurgical Institute. Our recommendations regarding surgical treatment for patients with cerebral aneurysms were aimed at providing recommendations on justified selection of each of these techniques. In this regard, our publication was based on tense discussions about the shortcomings and advantages of different treatment methods. The solution of this problem is extremely important to validate the indications for surgical treatment of patients with asymptomatic cerebral aneurysms and aneurysms in the cold period after spontaneous intracranial hemorrhage (Fig. 2 and 3) adopted at the Burdenko Neurosurgical Institute are described below.

### Discussion

There are Russian and international publications [8—10] focusing on the problem of assessing the risk of the UAA rupture, but there is no uniform and generally accepted point of view on this issue. The solution of this problem is extremely important to validate the indications for surgical treatment of patients. Decision on the need for surgical treatment raises the question of treatment method. We found no generally accepted criteria for choosing the method of surgical treatment of patients with cerebral aneurysms in the literature. It is known that in France, almost all aneurysms are excluded from the bloodstream using the endovascular technique, while in Finland the situation is quite opposite. In the US and Germany, there are intense discussions about the shortcomings and advantages of each of these techniques. In this regard, our publication was aimed at providing recommendations on justified selection of surgical treatment for patients with cerebral aneurysms used at the Burdenko Neurosurgical Institute. Our recommendations are based on the characteristics of the clinical course of the disease as well as anatomical and morphological characteristics of aneurysms, and their effectiveness was verified and validated based on clinical experience. Clinical Recommendations for the Treatment of Unruptured Asymptomatic Cerebral Aneurysms is a recent publication issued in 2016, which is the most similar one to our recommendations [10].

In this study, we combined two groups of patients: those with asymptomatic unruptured aneurysms and aneurysms in the cold period (in 3 months) after spontaneous intracranial hemorrhages. As shown earlier, these groups differ dramatically in terms of the clinical course of the disease. As for the surgical aspects, the principles of selecting the method and tactics of surgical treatment of patients with single and multiple aneurysms are similar. The need for surgical treatment of aneurysms in the cold period after spontaneous intracranial hemorrhages is beyond doubt. In the case of single or multiple asymptomatic aneurysms, the decision on the need for surgical treatment of the patient is not so indisputable and depends on many factors, where patient’s age, medical status, the presence of concomitant diseases, location, size, and configuration of the aneurysm (aneurysms) are the most important ones. These issues were quite often discussed in detail in Russian and international literature. Based on the experience accumulated at our center, we usually incline to the opinion that surgical treatment is required and our choice is validated by very convincing results of surgical treatment of patients with asymptomatic cerebral aneurysms (Table 1).

Postoperative mortality was 4 (0.25%) of 1621 patients who were operated on, which agrees with the literature data (0.25—0.27%) [11, 12].

Application of treatment algorithms described in the article for treatment of patients with cerebral UAAAs and aneurysms in the cold period after SAH (Table 2) is justified in clinics with microsurgical and endovascular units, specializing in the treat-
ment of patients with cerebral aneurysms and equipped with high-tech equipment and staffed by qualified specialists.

The data shown in Tables 1 and 2 demonstrate the effectiveness of our algorithms for surgical treatment of patients with UAAs and with aneurysms in the cold period after spontaneous intracranial hemorrhages.

Of cause, the aforementioned algorithms are not a dogma and there are some factors that can affect the tactics and choice of the method of surgical treatment in individual cases. At the same time, the diversity of clinical anatomical situations and exceptions that are admissible in some cases do not contradict the key principles that we have developed and we believe that they justify the most appropriate vector of treatment for this contingent of patients.

Authors declare no conflict of interest.

Table 1. The results of surgical treatment of patients with cerebral UAA at the Burdenko Neurosurgical Institute

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of operated patients</th>
<th>Number of patients with multiple CAs, abs. (%)</th>
<th>Direct operations</th>
<th>Endovasal operations</th>
<th>Combined operations, abs. (%)</th>
<th>Number of complications, abs. (%)</th>
<th>Postoperative lethality, abs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>82</td>
<td>16 (19.5)</td>
<td>57</td>
<td>25</td>
<td>0</td>
<td>13 (15.9)</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>77</td>
<td>18 (23.4)</td>
<td>51</td>
<td>26</td>
<td>1 (1.3)</td>
<td>12 (15.6)</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>85</td>
<td>16 (18.8)</td>
<td>61</td>
<td>24</td>
<td>2 (2.4)</td>
<td>15 (17.6)</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>167</td>
<td>37 (22)</td>
<td>104</td>
<td>63</td>
<td>3 (1.8)</td>
<td>14 (8.4)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>2013</td>
<td>224</td>
<td>44 (19.6)</td>
<td>121</td>
<td>103</td>
<td>9 (4)</td>
<td>20 (8.9)</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>255</td>
<td>55 (21.6)</td>
<td>131</td>
<td>124</td>
<td>12 (4.7)</td>
<td>9 (3.5)</td>
<td>0</td>
</tr>
<tr>
<td>2015</td>
<td>205</td>
<td>43 (20.1)</td>
<td>114</td>
<td>91</td>
<td>11 (5.4)</td>
<td>8 (3.9)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>2016</td>
<td>260</td>
<td>47 (18)</td>
<td>159</td>
<td>101</td>
<td>13 (5)</td>
<td>16 (6.2)</td>
<td>0</td>
</tr>
<tr>
<td>2017</td>
<td>266</td>
<td>53 (20)</td>
<td>168</td>
<td>98</td>
<td>17 (6.4)</td>
<td>17 (6.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1621</td>
<td>329 (20.2)</td>
<td>966 (59.5)</td>
<td>655 (40.4)</td>
<td>68 (4.1)</td>
<td>124 (7.6)</td>
<td>4 (0.25)</td>
</tr>
</tbody>
</table>

Table 2. The results of surgical treatment of aneurysms in the cold period after spontaneous intracranial hemorrhage

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of operated patients</th>
<th>Number of patients with multiple CAs, abs. (%)</th>
<th>Direct operations</th>
<th>Endovasal operations</th>
<th>Combined operations, abs. (%)</th>
<th>Number of complications, abs. (%)</th>
<th>Postoperative lethality, abs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>206</td>
<td>47 (22.8)</td>
<td>173</td>
<td>26</td>
<td>7 (3.4)</td>
<td>20 (9.7)</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>189</td>
<td>37 (19.6)</td>
<td>151</td>
<td>38</td>
<td>5 (2.6)</td>
<td>31 (16.4)</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>193</td>
<td>36 (18.7)</td>
<td>142</td>
<td>51</td>
<td>8 (4.1)</td>
<td>30 (15.5)</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>163</td>
<td>35 (21.5)</td>
<td>129</td>
<td>34</td>
<td>7 (4.3)</td>
<td>21 (12.9)</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>215</td>
<td>45 (20.9)</td>
<td>177</td>
<td>38</td>
<td>10 (4.7)</td>
<td>9 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>250</td>
<td>56 (22.4)</td>
<td>194</td>
<td>56</td>
<td>17 (6.8)</td>
<td>11 (4.4)</td>
<td>0</td>
</tr>
<tr>
<td>2015</td>
<td>215</td>
<td>53 (24.7)</td>
<td>172</td>
<td>43</td>
<td>18 (8.4)</td>
<td>19 (8.8)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>2016</td>
<td>222</td>
<td>51 (23)</td>
<td>145</td>
<td>77</td>
<td>15 (6.8)</td>
<td>15 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>2017</td>
<td>314</td>
<td>76 (24.2)</td>
<td>222</td>
<td>92</td>
<td>23 (7.3)</td>
<td>22 (7)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>1967</td>
<td>436 (22.1)</td>
<td>1505 (76.5)</td>
<td>455 (23.0)</td>
<td>110 (5.6)</td>
<td>178 (9)</td>
<td>3 (0.15)</td>
</tr>
</tbody>
</table>

REFERENCES


The authors draw our attention the algorithm that they developed for the surgical treatment of two groups of patients with intracranial aneurysms: asymptomatic ones without signs of rupture and ruptured aneurysms in the so-called cold period of the disease. The development of this algorithm is based on extensive experience in microsurgical and endovascular operations, accumulated at the Burdenko Neurosurgical Institute. The algorithm was developed on the basis of the analysis of the results of treatment of 1621 patients with unruptured asymptomatic aneurysms and 1967 patients with ruptured aneurysms operated on in the cold period of the disease. The presented algorithm can be regarded as a recommendatory protocol for managing the aforementioned categories of patients. In this regard, the practical value of this work is obvious. The scientific novelty of this study should also be noted, including systematization of extensive and representative clinical material, which allowed authors to validate to the reliability of the results.

A.S. Saribekyan (Moscow, Russia)
The advent and development of innovative minimally invasive technologies have initiated rapid development of endovascular surgery around the world, which enables prompt examination and treatment of patients with vascular pathology of the spinal cord. Spinal angiography and endovascular embolization of spinal vascular lesions have been extensively used in clinical practice and improved at the Burdenko Neurosurgical Institute.

SDAVF was characterized as subacute necrotizing myelitis as early as 1926. C. Foix and Th. Alajouanine [1] reported two autopsy studies that revealed advanced pathological dilation of spinal vessels with small vein thrombosis and numerous necrotic foci within the medullary substance.

In 1966 and 1978, K. Jellinger [2, 3] analyzed the results of 60 autopsies and concluded that SDAVF was a specific form of chronic radicular myelopathy associated with vascular disorders of the spinal cord. Spinal angiography and endovascular embolization of spinal vascular lesions have been extensively used in clinical practice and improved at the Burdenko Neurosurgical Institute.

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By using selective spinal angiography, B. Kendall and V. Logue [6] (1977) found that the fistula may occur not in the substance or on the surface of the spinal cord but in the dural nerve root cuff, which became the basis for the modern anatomical concept of SDAVF.

The incidence rate of SDAVF is low: 5—10 new cases of the disease per 1 million population per year [7]. The disease manifests itself by severe neurological symptoms leading to disability.

Material and methods

Over the last 5 years (2013—2017), 286 patients with SDAVFs were diagnosed and treated at the Neurosurgical Institute. There were 82% of males and 18% of females (5:1 ratio); the mean age was 51 years. The endovascular technique was used in 279 patients. All patients underwent total selective spinal angiography in order to study angioarchitectonics and to choose an endovascular treatment option.

Results and conclusion. Endovascular embolization of fistulas was performed in 295 out of 302 patients; direct surgery was used in the remaining cases. Endovascular treatment provided total SDAVF occlusion in 78% of cases and partial SDAVF occlusion in 22% of cases. Long-term outcomes were followed-up in all patients in a period of 6 to 12 months. In 90% of cases, improvement or stabilization of neurological symptoms was observed. In 60% of cases, there was a marked improvement in the neurological status in the form of rapid (within a few days) recovery of lost motor functions. The remaining patients had stabilization of clinical symptoms.

Keywords: spinal dural arteriovenous fistula, myelo-ischemia, symptoms, embolization, outcomes.

Abbreviations:

AVM — arteriovenous malformation
MRI — magnetic resonance imaging
PVAE — polyvinyl acetate embolus
SDAVF — spinal dural arteriovenous fistula
DM — dura mater
angioarchitectonics and choose the endovascular treatment option.

The distribution of SDAVs by location was as follows: thoracic spinal cord level — 196 (68.5%) patients, lumbar level — 76 (26.5%) patients, and lumbosacral level — 14 (5%) patients. The usual age of disease manifestation was 50—60 years.

Pathogenesis and structure of SDAVF

SDAVF is an abnormal arteriovenous shunt between the meningeal branch of a short posterior radicular artery and the posterior spinal vein at the intervertebral foramen level. The afferent vessel originates from the posterior trunk of the intercostal artery and connects to the meningeal vein [8―11].

In contrast to the arteries, the spinal cord veins can penetrate through the DM at a considerable distance from the nerve root [12]. In most cases, the extradural afferent vessel is the origin of a shunt that is located within the DM and opens to the draining vein. Further, pressure in the posterior spinal vein is increased, and the vein is widened.

Venous hypertension leads to a decrease in the arteriovenous pressure gradient and a reduction in perfusion, which is accompanied by progressive spinal cord hypoxia. Increasing venous pressure further reduces blood flow, causing progressive intramedullary vasodilation, which leads to depletion of the autoregulation system in affected areas of the spinal cord, development of edema, and, finally, dysfunction of the spinal cord conduction pathways [13, 14].

SDAVF may be highly suspected based on clinical data and MRI findings. The MRI signs characteristic of SDAVF include spinal cord signal enhancement at the thoracic level on a T2-weighted image caused by venous ischemia; identification of tortuous vessels in the posterior subarachnoid space of the spinal cord (Fig. 1).

The final stage in the diagnosis of SDAVF is selective spinal angiography that identifies sources of blood supply to SDAVF and the direction of venous outflow.

The afferent meningeal artery may have a multibranch structure. An arteriovenous shunt may also be formed by meningeal branches of several radicular arteries due to the existence of interarterial meningeal anastomoses. These fistulas are referred to as multichannel pathways [13, 14].

SDAVF feeding vessels within pathologic veins, we usually used adhesives histoacryl or N-butyl cyanoacrylate mixed with lipiodol in 89% of cases. Adhesives were injected directly into the SDAVF area using microcatheters. To prevent microcatheter thrombosis, 2.0 mL of a 5% dextrose solution was injected before embolization. To embolize the SDAVF feeding vessels within pathologic veins, we usually used adhesives histoacryl or N-butyl cyanoacrylate mixed with lipiodol in 89% of cases. Adhesives were injected directly into the SDAVF area using microcatheters. To prevent microcatheter thrombosis, 2.0 mL of a 5% dextrose solution was injected before embolization.

Clinical picture

On the basis of clinical material analysis, we have concluded that spinal cord lesion in SDAVF develops slowly: venous thrombosis and hypertension that underlie venous myelo-ischemia develop within 1 to 3 years.

The disease usually begins with hypoesthesia, followed by lower limb weakness and genitourinary system disorders. At the disease onset, some patients reported ascending loss of sensation in the setting of radicular pain syndrome (30%). By the time of treatment, patients experienced lower limb weakness of varying severity, sensoric disorders, and pelvic disorders in the form of urinary retention or incontinence. Impotence occurred in all patients. Neurological symptoms progressed steadily in all patients. Every 8th patient developed paraplegia. The disease symptoms corresponded to the affected spinal cord level. In the case of myelo-ischemia in the medullary cone region, the first disease manifestations included sensory disorders and episodic symptoms of urinary retention or incontinence. Later, hyperreflexia, pronounced asymmetric paraparesis, and muscle-joint sensation impairments developed. It should be noted that there were no hemorrhages associated with SDAVF.

Results of SDAVF treatment using adhesive glues

Endovascular treatment of 279 patients with adhesives (n-butyl cyanoacrylate) and non-adhesives (Onyx-18, Phil) led to total occlusion of SDAVF in 78% of primary treatment cases and to partial occlusion in 22% of cases. Repeated embolizations were required in 10% of cases.

Neurological symptoms improved or stabilized in 90% of cases. Postoperative recovery usually started with recently developed symptoms. In 60% of cases, there was a significant improvement in all types of disorders. Just a few days after endovascular embolization, during hospital stay, patients could walk without assistance. In the remaining patients, progressive myelo-ischemia stabilized, or long-term rehabilitation treatment was required. In spite of the prolonged disease duration in a group of patients with paraplegia, pressure ulcers healed; urinary function and general condition improved; in some cases, motions developed, which promoted body verticalization. Recovery of sensory disorders was less satisfactory.

In our study, SDAVs were verified in 14 patients; the afferent vessel of SDAVF was the lateral sacral artery that connected to the vein at the L5—S1 level and run upward to the cervical segment level, causing edema at the lower thoracic cord level (Fig. 3).
administration of the adhesive. In 10 cases, we used 100 to 500 µm polyvinyl acetate (PVA) emboli. In some cases, it was necessary to occlude the intercostal arteries and sometimes subjacent or opposite arteries with visible anastomoses.

In the presence of massive collateral vessels between the superjacent and subjacent intercostal arteries, additional embolization of the anastomosing branches was performed.

On a follow-up examination performed in all patients 1 year after surgery or upon worsening of the condition, a new shunt may be identified, which was formed due to pre-existing neighbor anastomoses. In these cases, all visible collaterals were embolized using the most appropriate methods (Fig. 4).

In 6 cases after PVA-based embolization, repeated endovascular surgery was performed due to recanalization and worsening of neurological symptoms in the postoperative period. In these cases, a combined technique was used: PVA-based embolization and adhesive glues.

When the anterior spinal artery and the SDAVF feeding vessels simultaneously originate from the intercostal artery, open surgery might be used; however, the endovascular surgical technique usually enabled super selective exclusion of the fistula, bypassing a normal spinal vessel.

A microcatheter was placed in the afferent vessel, and adhesives were injected until the level of entrance to the pial vascular network, until the medullary veins were reached (Fig. 5).

If super selective catheterization of the arteriovenous shunt area distal to the anterior spinal artery origin was not possible, direct surgery was used.

It should be noted that there were no surgical complications in the study group.

Control postoperative T2-weighted MRI of the spinal cord 1 year after surgery demonstrated that an initially enhanced signal from affected areas of the spinal cord gradually decreased or disappeared completely (Figs. 6, 7).

During SDAVF embolization, heparin therapy was performed under control of the blood coagulation system. After discharge, antiplatelet and vascular therapy was recommended in 80% of cases. These recommenda-
tions were based on the fact that SDAVFs were part of a complex progressive thrombotic spinal cord disease associated with changes in the spinal cord not only in the thoracic region but also at the lumbar enlargement, medullary cone, and cauda equina level.

It should be noted that all patients who received long-term glucocorticosteroid therapy at their place of residence developed sharp deterioration of neurological symptoms up to paraplegia, urinary retention, and trophic skin changes in the sacrum region. We related deterioration of the condition to increased venous ischemia of the spinal cord and thrombosis of small veins. The literature data [16] also confirm our negative opinion about steroid therapy. In these patients, T2-weighted MRI revealed more disseminated myelo-ischemia compared to the baseline level. In these patients, despite endovascular surgery, edema persisted for a long time, and regression of neurological symptoms was slower than usual.

**Discussion**

In the discussed cases, every 2nd patient was erroneously diagnosed at a local hospital: the most often diagnosis was herniation or protrusion of the intervertebral disc; appropriate treatment was performed; in some cases, surgery was carried out. The second diagnostic error was the diagnosis of infiltrative astrocytic tumor, then multiple sclerosis, and impaired spinal circulation with the development of myelitis.

In SDAVF, the spinal cord is extensively damaged, so neurological symptoms, such as lower paraparesis, conductive hypoesthesia, and urinary retention, in pa-
Patients aged 50—70 years should suggest the diagnosis of a dural fistula. Therefore, SDAVF is a progressive disease characterized by gradual involvement of the spinal cord, development of paraplegia, and pelvic dysfunctions. Patients without timely endovascular surgical treatment develop transverse atrophy of the spinal cord.

After many years of observation and treatment of SDAVF patients, we have come to the conclusion that the earlier the diagnosis, the more effective the endovascular treatment, which facilitates rapid recovery of lost spinal cord functions. Even in cases when the disease has caused irreversible changes in the spinal cord, endovascular embolization followed by medication and rehabilitation treatment stops the necrotic process in the spinal cord and provides favorable conditions for its recovery.

At the initial disease stage, the effect of endovascular treatment was always significant and noticeable; patients marked improvement immediately after surgery, especially in the motor functions and then improvements in the genitourinary system. This is associated with the fact that endovascular embolization with preservation of the posterior spinal vein preserves normal venous drainage of the spinal cord. In this case, blood pressure in the venous system decreases, and, importantly, diapedetic hemorrhages from dilated tortuous veins are excluded, which facilitates rapid functional recovery. Further, patients receive active rehabilitation treatment, including drugs that affect blood clotting.

According to the literature data [17], success rates for adhesive glues are 70—90%. For non-adhesive glues, the success rate approaches 90—95%. Our experience in treating 20 patients indicates that the use of non-adhesive

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**Fig. 5. Endovascular exclusion of a SDAVF at the T9 level.**

a — a SDAVF is fed by a short tortuous afferent vessel at the T9 level on the left. At the same level, the large radicular artery (a. Adamkiewicz) branches from the intercostal artery; b — selective catheterization of the SDAVF with a microcatheter distal to the large radicular artery (a. Adamkiewicz); c — the SDAVF is excluded from the circulation, with the large radicular artery (a. Adamkiewicz) being preserved.

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**Fig. 6. Changes in the spinal cord after exclusion of a SDAVF on the thoracic level.**

a — T2-weighted MRI scan before surgery: an elevated signal is observed at the level of six vertebrae. The subarachnoid space is narrowed; single dilated vessels are seen on the posterior surface of the spinal cord; b — T2-weighted MRI scan 1 year after endovascular surgery: there is no spinal cord edema; the subarachnoid space is normal. The patient achieved complete clinical recovery.
Conclusion

The main task for successful endovascular treatment of a SDAVF is to embolize the arteriovenous shunt area with preservation of draining veins. For this purpose, selective catheterization of the radicular arteries is used.

In the case of multichannel blood supply to a SDAVF, embolization should be performed differentially, based on evaluation of all vessels involved in the blood supply to both the fistula and the spinal cord.

The clinical efficacy of endovascular surgery is assessed based on patient’s neurological functions in the postoperative period. In our series, significant regression of neurological symptoms was achieved in 90% of cases.

Modern techniques of SDAVF embolization are adequate treatments that very efficiently eliminate pathological effects on the spinal cord. It is important to note the importance of early diagnosis because early treatment directly affects the disease outcome. The probability of recovery is high in general, but the best outcomes are achieved in patients with the shortest period between the onset of first disease symptoms and endovascular treatment.

Authors declare no conflict of interest.
The article is devoted to endovascular surgery of spinal dural arteriovenous fistulas (SDAVFs) manifested by severe neurological symptoms including paresis, sensory disorders, urinary system disorders, etc. The topicality of the problem is beyond doubt because SDAVF is the most frequent manifestation of vascular pathology of the spinal cord (up to 80% of all spinal vascular malformations). This pathology is not only hard-to-treat but also cannot be always correctly diagnosed by experts.

The recent development of neuroimaging techniques (MRI, MR-angiography, SCT angiography) has led to more often diagnosis of this pathology and raised the issue of appropriate management. In the article, the authors clearly indicate the urgent need in endovascular embolization when the first symptoms of the disease appear, which significantly improves the prognosis. The main goal of surgery is to embolize the arteriovenous shunt with preservation of the arteries supplying blood to the roots and spinal cord as well as to the draining veins involved in the spinal blood circulation.

The presented group of patients is large and heterogeneous. The clinical picture of the disease, vascular anatomy of the spinal cord, and DAVF angioarchitectonics are described in detail. Endovascular treatment was aimed directly at eliminating the pathophysiological mechanisms of spinal cord lesion. Preoperative examination was aimed at assessing the affected spinal cord level. All patients underwent selective spinal angiography, and its findings were used to choose an endovascular technique for SDAVF exclusion. In this case, the issues of choosing endovascular instrumentation and adhesive glues for embolization are discussed in detail. A good clinical outcome was achieved in all cases.

Therefore, the authors have demonstrated that comprehensive diagnostics and timely endovascular surgery limit treatment in most cases to minimally invasive intervention, avoiding traumatic open surgery.

The paper is of great interest both for neurosurgeons and interventional neuroradiologists and for neurologists who are at the first line of diagnosis of the extremely complex vascular pathology such as SDAVF.

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Intra-Arterial Administration of Verapamil for Prevention and Treatment of Cerebral Angiospasm After SAH Due to Cerebral Aneurysm Rupture

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Aim — the study purpose was to analyze the efficacy of intra-arterial administration of verapamil (IAV) in the treatment of angiospasm in SAH patients and to determine optimal parameters of the procedure. A number of studies demonstrated the efficacy of intra-arterial administration of vasodilators, in particular verapamil, in the treatment of angiospasm after aneurysmal SAH, which served the basis for inclusion of this method in the recommended protocol for treatment of SAH patients [1―7].

Material and methods. We analyzed the efficacy of IAV in 35 patients in the acute period of SAH, with 77.2% of the patients having a Hunt-Hess score of III―V. The inclusion criteria were as follows: IAV within two weeks after SAH; excluded aneurysm; verapamil dose per administration of at least 15 mg; follow-up for at least three months. Efficacy endpoints were as follows: changes in spasm according to angiography and transcranial dopplerography (TCDG); development of ischemic lesions; clinical outcome according to the modified Rankin scale.

Results. A total of 76 IAV procedures were performed. The verapamil dose per procedure was 36.7±9.7 mg, on average; the number of procedures varied from 1 to 5. One arterial territory was treated in 12 cases, two arterial territories were treated in 48 cases, and three arterial territories were treated in 15 cases. Typical adverse reactions included decreased blood pressure, a reduced heart rate, and elevated ICP. In all cases, TCDG revealed signs of reduced angiospasm ― a 20―40% decrease in the LBFV in the M1 MCA. Four (11.4%) patients died; of these, only one died due to angiospasm progression. On examination at 3 months or more after discharge, favorable outcomes were observed in 74.3% of cases.

Conclusion. IAV is associated with a low risk of significant complications. IAV should be performed under control of systemic hemodynamics and ICP. The indications for IAV include signs of moderate worsening or severe angiospasm according to TCDG and/or angiography. The IAV procedure may be performed every day. Further clarification of the IAV procedure and evaluation of clinical outcomes under prospective study conditions are required.

Keywords: SAH, angiospasm treatment, intra-arterial administration of verapamil.

Abbreviations:
ICH — intracerebral hematoma
ICA — internal carotid artery
ICP — intracranial pressure
DC — decompressive craniectomy
IAV — intraarterial injection of verapamil
LBFV — linear blood flow velocity
MA — major artery
AMA — anterior cerebral arteries
SAH — subarachnoid hemorrhage
SCT-AG — spiral computed tomography angiography
MCA — middle cerebral artery
TCDG — transcranial dopplerography

Spasm of cerebral vessels with subsequent delayed cerebral ischemia is one of the leading issues in treatment of patients in the acute period of aneurysmal subarachnoid hemorrhage (SAH), which significantly worsens the clinical outcome [1]. Various methods of prevention and treatment of angiospasm have been tested in both clinical and experimental conditions, but none of them has been recognized as highly effective and sufficient [2, 3]. This justifies further search for ways to prevent and treat this complication of SAH.

A number of works [4―7] with encouraging results demonstrated the use of intra-arterial administration of vasodilating drugs, in particular verapamil. However, at the moment there is no single protocol for intraarterial administration of verapamil (IAV) with clear recommendations on the time of initiation of the therapy, mode and multiplicity of administration, and other features of the methodology. Nevertheless, the positive effect of intraarterial administration of various antispasmodic drugs, which was achieved in sufficiently large cohorts of patients, allowed this method to be included in the latest published recommendations for the treatment of patients with SAH (class IIa, level of evidence B) [2].

IAV method has been used in the Burdenko Neurosurgical Institute for the last 5 years.
Materials and Methods

In the period of 2012—2017, IAV was performed in 42 patients who were admitted to the hospital in the acute period following a hemorrhage from an aneurysm of the cerebral vessels. In each case the drug was administered off-label after obtaining the permission of the Burdenko Neurosurgical Institute ethical committee, the decision was made by a medical commission.

The inclusion criteria were as follows: the first (or the only) verapamil administration no later than within two weeks after the last SAH; total verapamil dose per administration of at least 15 mg; follow-up for at least three months after discharge.

In accordance with these criteria, 35 patients were included in the retrospective analysis group. Their average age was 46.7±14.5 years (from 8 to 77 years), the ratio of men to women was 13/22. Aneurysms were localized as follows: ICA — 7, MCA — 7, AMA — 19, MA — 2. Preoperative assessment and further management of patients were carried out in accordance with the general principles of patient management in the acute period of SAH: assessment on the Hunt-Ness scale upon admission; CT of the head upon admission and in dynamics, with the assessment of the hemorrhage based on Fisher Grading Scale, identification of ischemic foci and their characteristics. Diagnosis and determination of angiospasm severity was performed based on the data of diagnostic selective cerebral angiography (AG) or SCT-AG, as well as on the data of daily TCDG. Aneurysm clipping was performed in all patients (in 26 cases the technique was microsurgical, in 9, endovascular); auxiliary surgeries were performed according to the indications: EVD, DC. The treatment was carried out in the intensive care unit with monitoring of the main homeostasis indices. If indicated, a parenchymal sensor was installed to monitor ICP [8].

IAV was performed after the aneurysm was clipped. Indications for IAV and features of the technique are described in the “Results” section. The following data were recorded during IAV: the day of the first procedure in relation to SAH; single dose and total amount of the drug; parameters of systemic hemodynamics during the procedure; dynamics of TCDG data; dynamics of neurological status; dynamics of the state of the brain according to CT; dynamics of the spasm according to AG. Calculation of the degree of the vessel constriction was made in percents relative to the average standard diameter. For ICA the value is 4 mm, for MCA it is 3.2 mm, for the largest AMA it is 2.6 mm and for MA it is 3 mm [9, 10]. Depending on the degree of narrowing of the artery lumen, angiographic spasms were classified as light (up to 30% of diameter), moderate (30—60%) and pronounced (more than 60%) [7]. By analogy with the indices of arterial stenosis, which are used to determine indications for carotid endarterectomy, a group with a pronounced narrowing of the lumen of the vessels of more than 70% was identified.

Efficacy endpoints were as follows: dynamics of the spasm according to angiography, immediately after the drug administration and delayed (the latter, in case of repeated AG); dynamics of the spasm according to transcranial dopplerography (TCDG, 1 hour after the procedure and delayed); development of ischemic lesions during or after the end of the verapamil treatment (increase in size and appearance of new foci in case of pre-existing foci); onset of delayed neurological deficit. Modified Rankine scale (mRs) [11] was used to assess the outcome at the time of discharge and 3 months or more after the discharge.

Results

The patients’ characteristics prior to the surgery:

The condition of most patients before the surgery was severe; in 77.2% of cases it was assessed as grade III-V according to Hunt-Ness scale. In 90.6% of patients, the massiveness of SAH corresponded to grade III—V according to Fisher Grading Scale (Table 1).

All patients underwent surgery on the aneurysm no later than 14 days after SAH. Median time for the surgery: day 4. In 12 cases, the primary DC was performed during the surgical intervention on the aneurysm, in 3 cases, the DC was delayed according to vital indications. Thus, DC was performed in 40% of patients. In 14 (40%) patients, EVD was used for the first few days after the surgery. Verapamil was administered intraoperatively in 3 out of 9 (33%) cases of endovascular operations after the occlusion of the aneurysm.

Characteristics of the patients after the surgery and indications for IAV

Indications for IAV were elucidated based on postoperative assessment and dynamics of clinical and instrumental signs of angiospasm.

Assessment of the clinical state of the patient at the time of the first IAV procedure provided little information, as many patients were in a state of medical sedation. Nevertheless, verapamil was administered to 9 patients due to apparent clinical deterioration. The assessment was based on such clinical signs as the emergence/growth of cerebral or focal symptoms in the absence of any other causes of deterioration (ICH, hydrocephalus, etc.). Intraoperative visualization of angiospasm was also taken into account. In other cases, we focused on the instrumental indices of angiospasm: Indications for initiation of IAV course were signs of a moderate but rapidly increasing angiospasm and signs of pronounced angiospasm according to the TCDG data [12].

Prior to IAV, ischemic foci were detected in 8 patients using CT. Of these, the foci were regarded as caused by angiospasm (not associated with intraoperative damage of any artery) in 7 cases. Ischemic foci associated with clipping or stenosing of the artery during surgery were identified in 3 patients. An independent evaluation
by two researchers produced a consensus on characteristic of etiopathogenesis of ischemia foci.

**Drug dosage and administration procedure**

In case of clinical and/or dopplerographic signs of angiospasm, standard selective cerebral AG was performed and upon the confirmation of angiospasm selective IAV was performed in spasmomd arteries. Verapamil was administered at a concentration of 0.25 mg/mL at an average rate of 10 mL/min. The permissible range of the administered dose for the procedure was determined after the review of available literature on the intra-arterial administration of the drug (see "Discussion" section; Table 5). The drug dosage was chosen arbitrarily and depended on the severity of the vasospasm, but was at least 15 mg per procedure and averaged 36.7±9.7 mg (15 to 50 mg). The drug was administered in a manual mode, guided by the data of systemic hemodynamics monitoring, intracranial pressure, and clinical response of the patient.

The first IAV procedure was performed at various time points after SAH, in the period from 2 to 14 days. The average duration till the first IAV was 7.4±3.2 days. Number of IAV procedures ranged from 1 to 5 (Table 2). Repeated catheterization of the femoral artery was used, as well as an introducer, with daily saline washing. There were no complications related to these procedures. A total of 76 IAV procedures were performed. For most patients with repeated IAV, the procedure was performed on a daily basis. In some cases of the compensated state after the first procedures, the next IAV could have been performed in 1—3 days. Thus, the maximum duration of treatment was 8 days. The total dose of verapamil during the course averaged 78.6 mg (15 to 220 mg), the median one was 55 mg (32.5, 107.5 mg). In a number of cases, verapamil was administered only to the arterial territory, in other cases in was administered to all territories. One arterial territory was treated in 12 cases, two arterial territories were treated in 48 cases, and three arterial territories were treated in 15 cases.

**Side effects and complications in IAV**

Changes in systemic hemodynamics typical for vasospasm were observed quite often during the administration of the drug in a form of lowering of blood pressure and bradycardia. The drop in systolic blood pressure of more than 11 mmHg and/or a decrease in heart rate of 5 bpm or more was observed in 43 (57.3%) patients; a drop in blood pressure of 50 mmHg, in 8 (10.7%); a decrease in heart rate by more than 20 bpm was also observed in 8 (10.7%) patients. These reactions also developed in patients who received inotropic support before and during the administration of verapamil. Additional vasopressors were injected in case of a decrease in blood pressure by more than 30% from the baseline. It should be noted that the duration of blood pressure drop did not exceed 1—2 min and no clinical complications associated with fluctuations in hemodynamic parameters were observed.

In 8 cases IAV was performed together with invasive ICP monitoring. In all cases, IAV was associated with an increase in ICP up to 10 mmHg from the baseline, which did not exceed 20 mmHg in all patients. In case of increase in blood pressure the following corrective methods were used: opening of EVD, if it had been installed; mannitol administration. These measures resulted in normalization of ICP. An uncontrolled rise in ICP up to 40 mmHg was observed in one case, which required urgent DC.

**Dynamics of angiospasm in IAV**

Calculation of angiographic spasm severity was performed in 30 out of 35 patients; reliable calculations were impossible in the remaining 5 patients due to technical issues. In all cases moderate or pronounced narrowing of the lumen of the main vessels was established. Severity of the spasm was assessed in the most spasmomd arterial territory based on the worst value observed during the treatment (Table 3). Along with this indicator, the severity of spasm in the MCA M1 segment was calculated for all patients. Angiographic spasm in the arteries of the 2nd and 3rd order was observed in 21 (70%) patients.

In 6 cases, the AG-control of the effectiveness of the IAV procedure was performed 30 minutes after the administration: in all cases there was an increase in the diameter of the vessel and improvement of cerebral perfusion (see Figure).

The effect of increasing the lumen of the vessels was more pronounced in the most spasmomd areas. In all cases TCDG performed within 1 hour after the procedure revealed a decrease in LBFV for MCA M1 by 20—40% compared to the baseline (on average, by 27%). This difference disappeared the next day.
The dynamics of angiographic spasm was evaluated in 16 cases of repeated administrations. There was an increase in spasm in 11 (68.8%) patients, and its steady regression after the procedures was reported only in 2 (12.5%) patients. Remarkably, in one of these 2 cases, the course of IAV was started on Day 10 and in the other on Day 13, i.e. at the time when the regression of the spasm can be caused by the natural course for this complication. New ischemic foci (delayed ischemia) after the onset of the IAV treatment occurred in 12 (34.3%) patients.

**Short- and long-terms outcomes of the treatment**

Treatment outcomes for 35 patients are presented in Table 4. At the time of discharge, favorable outcomes (0—3 on mRs) were reported for 10 (28.6%) patients.

A total of 4 (11.4%) patients died. Of them, only 1 died due to the progression of angiospasm in the MCA territory; in this case IAV course was initiated after the onset of a large ischemic focus on the background of the progression of angiospasm. Causes of death for the other 3 patients: postoperative ischemic changes in the brainstem of a patient with an aneurysm of MA, who was operated on endovascularly; severe somatic pathology; sepsis.

The condition of the majority of surviving patients improved in the long-term period. On examination at 3 or more months after discharge, favorable outcomes were observed in 74.3% of cases.

The comparison of outcomes based on different parameters revealed a number of facts.

There were no dependence of the short- and long-term outcomes on the severity of the state at admission on Hunt—Ness scale. It should be noted that none of 3 patients with Hunt—Ness grade V died. Out of 11 patients with Hunt—Ness grade IV—V, adverse outcomes (mRs 4—6) in the long-term period were observed in only 2 people.

The short-term outcomes in 8 patients who underwent IAV after the onset of secondary ischemic foci due to angiospasm were worse, but the difference was statistically insignificant at the level of the trend (\( p=0.09 \)). In the immediate postoperative period, each of them had a mRs score of 4 or higher. For 6 of these patients, the onset of new secondary ischemic foci or the expansion of the ischemia zone was observed during the treatment, which significantly distinguished this group from the remaining patients (\( p=0.01 \)). In the long-term period, 3 of them improved to mRs 3, however, the outcomes in this group remained worse than in patients without secondary ischemia before IAV, with the differences becoming more evident (\( p<0.05 \)).

Of 9 patients in whom IAV was initiated due to clinical deterioration, there was only 1 case when the immediate outcome of treatment could be called relatively satisfactory (mRs 3). There was also a significant difference in the immediate outcomes for this group of patients compared with the remaining patients (\( p<0.05 \)). Four of these patients had onsets of secondary ischemic foci after IAV.

When assessing the dependence of the outcome of the disease on the severity of angiospasm detected during angiography, a significantly worse result was observed in the near future in case of a narrowing of the vessel diameter in at least one arterial territory by more than 70% (\( p=0.02 \)). Attempts to use other criteria for evaluation of angiospasm (degree of less than 70%, only MCA M1 segment) did not reveal any correlations. Among 8 patients with moderate spasm only one developed secondary ischemic focus (12.5%), while among 22 patients with marked angiographic spasm secondary foci developed in 9 (40.9%). Of the 20 cases in which we recorded angiographic spasm of segments of the 2nd and 3rd order, there were 9 (45%) cases of secondary ischemic lesions that appeared after the initiation of the IAV course. There were no cases of secondary ischemia among patients without angiographic spasm of similar segments.

**Discussion**

The search for an effective method of treating angiospasm in patients after aneurysmal SAH is one of the most important tasks that need to be addressed. To date, there is no medical treatment that significantly and reliably affects the development and course of a vascular spasm [2]. Balloon angioplasty can be one of the effective methods of treating a local spasm. However, this technique is able to resolve only segmental spasm of sufficiently large vessels, but is ineffective in spasms of distal branches and is associated with rather high rate of complications: up to 7% [7, 13, 14].

The intra-arterial administration of spasmolytic drugs can quickly deliver the maximum concentration of

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**Table 2. Distribution of patients based on the number of IAV procedures**

<table>
<thead>
<tr>
<th>Number of IAV procedures per patient</th>
<th>Number of patients</th>
<th>A total number of IAV procedures</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
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</tr>
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<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
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<td>76</td>
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</table>

**Table 3. Severity of angiospasm based on angiography data**

<table>
<thead>
<tr>
<th>Severity of angiospasm</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA M1, AMA A1 and OA territories</td>
<td>Assessment of only MCA M1</td>
</tr>
<tr>
<td>Moderate 30—60%</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Pronounced 60—100%</td>
<td>24 (80)</td>
</tr>
<tr>
<td>Total</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Over 70%</td>
<td>17 (56.7)</td>
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<td></td>
<td>13 (43.3)</td>
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</table>
Dynamics of cerebral perfusion after the administration of verapamil.

a — subtractional left-sided carotid angiography, direct; b — lateral projection. Pronounced spasm (more than 70%) of the M1 segment of the left MCA. A typical sign of spasm is visible in the direct projection, intensive contrasting (hyperemia) of the lenticular-lateral arteries (indicated by an arrow); c — 2D AG perfusion before the administration of verapamil; d — 30 minutes after the administration of verapamil. There is an increase in volumetric blood flow in the MCA territory.

the drug directly to the spasmodic part of the vessel, which caused a number of studies to assess this type of treatment. Various drugs have been used for intra-arterial administration at different periods of time: papaverine, nimodipine, nicardipine, verapamil, milrinone, fasudil, colforsin daropat [15]. The availability of verapamil, its low price, the encouraging results of several studies with a low number of complications (see Table 5) are the factors that served as the basis for choosing this drug for our study.

Verapamil is an antiarrhythmic drug from the group of diphenylalkylamines of the class IV according to the Vogan-Williams classification. It belongs to the group of L-type potential-dependent calcium channels blockers, and has antiarrhythmic, anti-anginal and antihypertensive activity. In case of systemic administration (oral, intravenous) the drug acts primarily on the heart: suppresses the activity of the sinus and atrioventricular node, slows the conduction, increases the effective refractory period. Verapamil reduces the tone of the smooth muscles of the coronary and peripheral arteries, as well as the general peripheral vascular resistance, which makes it the drug of choice for treatment of vasospastic angina. For intravenous administration, the half-life is biphasic: early — about 4 minutes, terminal — 2—5 hours. After intravenous administration, the antiarrhythmic effect develops within 1—5 min, hemodynamic effects (vasodilation, lowering of the blood pressure) within 3—5 min and persist for 10—20 min [16, 17]. There are few known pharmacodynamic and pharmacokinetic features after intra-arterial administration. Based on animal experiments the effect of vasodilation develops after 30 minutes [18, 19]. Due to the temporary impact of vascular dilatation, a number of authors [19, 20] explain the positive effect of the administration of verapamil in SAH by its greater tropism to resistive arterioles (prearterioles). IAV for treat-
ment of angiospasm was first used in 1988 in cardiology for treatment of coronary artery spasm [21]. Later, cases of intracoronary administration of verapamil in acute coronary syndrome were described, leading to a statistically significant improvement in coronary blood flow [22]. For the first time, the influence of IAV on cerebral blood flow in humans was described by S. Joshi et al. in 1997 [23]. The first series of 29 patients who received an IAV course for cerebral angiospasm was published by L. Feng et al. in 2002 [4]. Five more describing similar series of observations were published later (see Table 5). In each of these studies, the authors selected the dose of verapamil somewhat arbitrarily. The recommended dose for intravenous administration is 5—10 mg [16]. In published studies, the dose varied from 3 to 360 mg per procedure when administered at different time intervals. Depending on the effect of treatment and the severity of spasm, the authors could repeat the procedure multiple times; e.g. in series by P. Jun et al. (UCSF Medical Center) [7], more than half of the patients underwent repeated administrations. E. Albanese et al. [6] used another approach: The patient was prescribed a multiple-hour infusion of verapamil solution supplemented with heparin. The following evidence of the effectiveness of IAV for the prevention and treatment of cerebral angiospasm is presented in the published works: angiographically confirmed dilation of arteries (especially maximal spasms) 20—30 min after the procedure and comparatively good clinical outcomes of the treatment (see Table 5). We were unable to find studies comparing the comparable groups of patients with the use of IAV and without it.

Based on the analysis of available literature and discussion of the technique, we came to the conclusion that bolus administration of verapamil in a single dose of up to 20 mg per carotid territory and up to 10 mg per vertebrobasilar territory is safer. It was decided to forgo the prolonged administration of verapamil at the current stage due to the possibility of thromboembolic complications. Thus, in our studies the maximum dose of verapamil for the procedure was 50 mg. In the case of moderate spasms, we used lower doses, especially at the initial stage of the study. In all 6 cases of angiographic control, the dilation of the observed segments after 30 min was recorded with a tendency towards greater effect on the spasmotic vessels, which is consistent with published literature data. A significant decrease in the blood flow velocity was also recorded in all cases using TCDG. However, according to both angiography and TCDG, in most cases the improvement was not present on the next day. Due to the obviously temporary effect of the procedure, we used repeated administrations of verapamil in 60% of cases [24, 25]. The decision on repeated administration of the drug was made on the basis of good tolerability of the procedure after a single administration and the appearance of ultrasound signs of angiospasm recurrence within a short time after the first administration of verapamil. In addition to TCDG, clinical data were also used to make the decision whether to repeat the procedure: clinical deterioration justified the continuation of the IAV. The results obtained allowed us to consider the daily IAV procedures to be justified, in contrast to the recommendations of P. Jun et al., who proposed to conduct the treatment every 3 days. Risks and technical difficulties of conducting IAV procedure several times a day, as well as those of the prolonged administration of the drug via a fixed catheter, in our opinion, exceed the possible benefits from such treatment regimens.

The described series included patients in rather severe state: Grade III—V on the Hunt—Hess scale in 77.2% of patients, grade III—IV on the Fisher scale, in 90.6%. Therefore, we believe that the results obtained (satisfactory outcome in 28.6% of cases at discharge and in 74.3% of cases in the long-term period) indicate the effectiveness of the IAV technique, but this provision requires confirmation in prospective studies. According to

### Table 4. Short- and long-term treatment outcomes, mRs score

<table>
<thead>
<tr>
<th>mRs score</th>
<th>Short-term outcome, patients</th>
<th>Follow-up &gt;3 months, patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs.</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>6 (death)</td>
<td>4</td>
<td>11.4</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100</td>
</tr>
</tbody>
</table>

*Footnote. *— death in the short-term period.
our data, the outcome of treatment is significantly affected by the presence of ischemic foci, formed before the initiation of verapamil. This is due both to irreversible brain changes at the ischemia sites, and to limited “therapeutic strength” of the bolus IAV technique in the event of an extended spasm, which is manifested as the formation of new foci. It also explains the worst outcomes of treatment in patients for whom IAV was started during the worsening of the clinical condition. The change in the diameter of the main vessels by the time of repeated administration of verapamil is a conditional indicator of the effectiveness of treatment, since unfavorable outcome can be associated with spasm of peripheral vessels. It made us think about the advisability of superselective catheterization of the branches of the main arteries for the administration of verapamil directly into spasmodic arteries. We would like to point out that the presence of secondary ischemic foci is not a contraindication to IAV. We believe that the procedure can stop the progression of the disease and is beneficial for the penumbra zone.

This series, as well as the published literature, demonstrate the minimal and controlled effect of IAV on systemic hemodynamics. Cases of uncontrolled increase in ICP had been described in several studies and occurred in our series as well [6, 7]. Therefore, in case of severe hemorrhages we recommend to conduct IAV with ICP monitoring. The risk of uncontrolled ICH in IAV is lower in patients with external ventricular drainage or under the conditions of performed decompressive craniectomy.

### Conclusion

The results of the retrospective analysis of IAV in 35 patients with aneurysmal SAH allows to make the following conclusions.

The IAV technique is simple and associated with low risk of significant complications. IAV should be conducted with monitoring of systemic hemodynamics and ICP. The effect of widening of the vessel with a single dose of 15 mg is obvious. A single administration of 50 mg does not lead to significant changes in systemic hemodynamics.

The indications for IAV include signs of moderate worsening or severe angiospasm according to TCDG, signs of angiospasm according to angiography. The main risk group for development of angiospasm are the patients with massive SAH (grade III–IV according to Fisher) and patients with grade III–V according to Hunt–Hess.

The first IAV in the risk group should be performed on the Day 3—4 day after SAH in order to prevent angiospasm. The drug should be injected into all vascular territories. The second administration in the case of clinical deterioration or instrumental signs of an increasing spasm should be performed the next day after the first intervention; in the case of a stable clinical situation and in the absence of acceleration of blood flow, according to TCDG, one day later. IAV procedures can be performed on the daily basis up to Day 7—9 after the hemorrhage.

The presence of formed foci of ischemia is not a contraindication for IAV, except for cases of expanded foci with edema and dislocation of the brain.

Outcomes of the disease indicate the clinical effectiveness of IAV.

Further clarification of the IAV procedure and evaluation of clinical outcomes under prospective study conditions are required. Due to the obvious impossibility of carrying out a randomized study, it is necessary to compare the large normalized series of patients who were or were not given this treatment.

### Authors declare no conflict of interest.

### Table 5. Published results on the use of IAV in patients with aneurysmal SAH

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of patients</th>
<th>Dose per procedure, mg</th>
<th>Evidence of efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Feng et al., 2002 [4]</td>
<td>29</td>
<td>3.1±0.3</td>
<td>In 10 cases, the control AG was performed 10—15 min after the procedure and the dilation of the spasmodic vessels was observed. In 5 of 17 cases, there was positive clinical dynamics after the administration of verapamil</td>
</tr>
<tr>
<td>A. Mazumdar et al., 2006 [24]</td>
<td>15</td>
<td>7.4 (2.5 to 10)</td>
<td>There were no differences in the diameter of the vessel before and after the administration. There was no time stamp for the control observation. There was no 20—30-minute waiting period after the administration of verapamil</td>
</tr>
<tr>
<td>J. Sehy et al., 2010 [25]</td>
<td>12</td>
<td>22±8, max — 30</td>
<td>Vessels, especially the spasm site, are significantly wider 20—30 minutes after the administration of 10 mg of verapamil</td>
</tr>
<tr>
<td>E. Albanese et al., 2010 [6]</td>
<td>12</td>
<td>Prolonged infusion of 20—50, on average, 164 (70—360) per procedure</td>
<td>In all cases angiographic resolution of the spasm was observed, including the widening of the peripheral channel. Good clinical outcomes</td>
</tr>
<tr>
<td>P. Jun et al. 2010 [7]</td>
<td>189</td>
<td>3—55 mg</td>
<td>Relatively good clinical outcomes: satisfactory outcomes in 115 (61%), unsatisfactory in 55 (29%)</td>
</tr>
</tbody>
</table>
**REFERENCES**


Received: 21.02.18

**Commentary**

Treatment of cerebral angiospasm after subarachnoid hemorrhage caused by the rupture of aneurysms remains a major problem, since angiospasm is one of the main causes of secondary cerebral ischemia. The proposed methods for prevention and treatment of angiospasm have not yet been effectively recognized by the medical community as highly effective and sufficient. Currently, the main modern endovascular methods of treating angiospasm, angioplasty and intra-arterial administration of calcium channel blockers, are rarely used in Russia.

The authors present their experience in treating angiospasm of cerebral vessels in a retrospective series of 35 patients with subarachnoid hemorrhages caused by a rupture of aneurysms, who were treated at the Burdenko Neurosurgical Institute during the period of 2012—2017 by the intraarterial injection of verapamil. Verapamil is an antiarrhythmic drug of Class IV and belongs to a group of L-type calcium channel blockers. It is used in cardiology for treatment of coronary arteries spasm, and there have been foreign publications on the use of verapamil in cerebral angiospasm since 2000. The authors report the apparent efficacy of intra-arterial administration of verapamil in treatment of angiospasm. The dosage of the drug was chosen empirically. The drug was administered in a manual mode, guided by the hemodynamic monitoring data during manipulations and the angiographic condition of the spasmodic vessel. I fully agree with the authors of the article on the need for further study and development of a protocol for intraarterial administration of verapamil in a large normalized series of patients.

V.A. Lazarev (Moscow, Russia)
Large and giant vertebrobasilar (VB) aneurysms manifested by brainstem compression symptoms are a rather rare pathology associated with unsatisfactory treatment results, which is due high traumatism of open surgery for the aneurysms of this region. Surgical intervention is also complicated due to the large volume of aneurysms located in the anatomically complex area and the small volume of the posterior cranial fossa [1—6]. The above-mentioned factors often make aneurysm clipping difficult and increase the risk of postoperative complications.

The aim of this study was to analyze the results of surgical treatment of vertebrobasilar (VB) aneurysms manifested by brainstem compression symptoms.

Material and Methods

The study included 8 patients operated on in the period between 2014 and 2017. All patients underwent intravascular intervention; two patients had open surgery at the second stage.

Results and conclusion. Intravascular intervention, both alone and in combination with open surgery, is effective treatment of VB aneurysms whose clinical picture is manifested by brainstem compression symptoms. The use of flow-diverting stents in most cases has provided good radicalness in the long-term period, without worsening the functional outcome. Treatment of fusiform aneurysms of the basilar artery trunk requires separate consideration and an individual approach due to a high risk of thrombosis of short branches feeding the brainstem.

Keywords: aneurysm, vertebrobasilar territory, compression.
associated with AVM in the early postoperative period. Implantation of a flow-diverting stent into the assisting stent (in order to optimize the position of the flow-diverting stent only in the artery defect area and optimize the position of the assisting stent (in a relatively stable region) in the upper third of the basilar artery) was planned in a patient with a fusiform aneurysm of the middle and lower thirds of the basilar artery trunk with a space-occupying effect on the pons varolii. In the early postoperative period (day 1), the patient developed symptoms of ischemic damage to the brainstem caused by thrombosis of the perforating branches of the basilar artery, which led to the patient’s death on the third day after surgery.

The second stage of surgery was performed, which included decompressive trepanation of the posterior cranial fossa and resection of the aneurysm sac, which had a compression effect on the brainstem, in 2 cases due to the remaining symptoms (Fig. 2).

Long-term results were monitored in 5 patients in the period of 3—48 months after surgery. Four patients experienced almost complete regression of the existing symptoms. According to the control cerebral angiography data, aneurysm was not embolized in 4 patients, and insignificant embolization was observed in 1 patient. All patients also underwent control MRI of the brain, which showed reduction in aneurysm in size in 3 patients and absence of changes in the size in 2 cases.

Discussion

Large and giant VB aneurysms are often manifested by symptoms associated with compression of the brainstem and cranial nerves [7], which can form a different clinical picture, including obstructive sleep apnea, the development of which is associated with compression of the medulla oblongata [8].

Open surgery on aneurysms of this localization is still considered a high-risk procedure due to the size of the aneurysm and the width of its neck, as well as the proximity of functionally important neural formations. Despite this, some authors successfully apply this method with good outcomes [7, 9, 10]. In our series, open surgery was performed in 2 patients and led to improved neurological status. However, it should be noted that surgery was performed due to the persistent severe neurologic symptoms following intravascular surgery.

An alternative to open surgery is endovascular intervention in the form of embolization of the aneurysm cavity with coils with or without stent assistance [11], deconstruction of the aneurysm-bearing artery or installation of a flow-diverting stent. However, the mass effect remains when using microcoils, which can lead to deterioration of the functional result in case of small dimensions of the posterior cranial fossa. In addition, the risk of hemorrhage recurrence or increase in the size of the aneurysmal sac is preserved after coil application [12, 13].

A number of authors [14] consider endovascular occlusion of the aneurysm-bearing artery as the method of choice and report good early- and long-term results of the surgery. No deconstructive surgeries were performed in our series. However, according to the data by S.R. Arustamyan et al. [15], lethality in deconstructive surgery for VB aneurysm is extremely high and reaches 42.8%. It should be noted that one cannot be always sure in its complete exclusion from the bloodstream based on the cerebral angiography data, even in case of an empty aneurysm. K. Iihara et al. [12] described a case of aneurysm increase in size after repeated intravascular interventions, during which first aneurysm and then the carrier artery were excluded from the bloodstream. Despite contrast enhancement of the aneurysm on angiography images, repeated control MRIs showed an increase in the

Results of the treatment of patients with large and giant VB aneurysms

<table>
<thead>
<tr>
<th>№</th>
<th>Localization</th>
<th>Type of surgery</th>
<th>Complications</th>
<th>Outcome (according to the Glasgow Outcome Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BA</td>
<td>FD</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>BA</td>
<td>FD</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>BA</td>
<td>AS + FD</td>
<td>Thrombosis of short branches</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>VA</td>
<td>FD</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>VA</td>
<td>AS + FD</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>PICA</td>
<td>Microcoils + open surgery</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>PICA</td>
<td>Microcoils</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>SCA</td>
<td>FD + open surgery</td>
<td>No</td>
<td>4</td>
</tr>
</tbody>
</table>

Footnote. BA — basilar artery, VA — vertebral artery, PICA — posterior inferior cerebellar artery, SCA — superior cerebellar artery, FD — flow diverter, flow-diverting stent, AS — assisting stent, stent used for assistance.
Fig. 2. Giant aneurysm of the right superior cerebellar artery.

a, b, c — MRI in coronary, sagittal and axial projections, T1WI mode. Giant aneurysmal sac roughly compressing the brainstem is visualized; d — SCT angiography, the white arrow indicates embolized part of the aneurysm; e — stage of resection of thrombotic masses from the aneurysm cavity. Intraoperative photography.

AS — aneurysmal sac, Cer — cerebellum; f — brain SCT after surgery, a significant decrease in the size of the aneurysmal sac is noted with a decrease in brainstem compression.

Fig. 3. Fusiform aneurysm of the right vertebral artery.

a, b, c — brain MRI, coronary, sagittal and axial projections, T1WI mode. Aneurysmal sac roughly compressing the brainstem is visualized; d — oblique projection cerebral angiography; e — cerebral angiography after stent installation (indicated by an arrow); f — control SCT-AG after 12 months.
aneurysm in size. The authors associate this phenomenon with a developed vasa vasorum network of the aneurysm walls and repeated intramural hemorrhages.

Flow-diverting stent implantation seems to be one of the most promising methods, but its application for the aneurysms of the basilar artery trunk still raises a number of questions [16, 17] due to the complicated prognosis of the preservation of branches feeding the brainstem. For instance, of 7 patients operated on using flow-diverting stents in the series of observations by A. Siddiqui et al. [16], there were 4 cases of death, while outcome in the remaining patients corresponded to 5, 1 and 0 according to the modified Rankin scale. There is also a high risk of postoperative hemorrhage from the aneurysm associated with rapid formation of a thrombus in the aneurysm cavity and aseptic inflammation of the vascular wall at the site of implantation in case of stent installation [16].

There were no complications noted after implantation of a flow-diverting stent into the basilar artery in our series (Fig. 3). However, thrombosis of the short branches of the basilar artery, which led to the death of the patient with fusiform aneurysm of the basilar artery, developed after stent implantation. This observation indicates the uncertainty of the use of stents in patients with vertebrobasilar aneurysms, as well as the need for an individual approach when choosing the treatment method for patients with such lesion.

Conclusion

Thus, a preliminary conclusion can be made on the possibility of a relatively safe application of intravascular surgery in patients with large and giant vertebrobasilar aneurysms. Treatment of fusiform aneurysms of the basilar artery trunk requires separate consideration. It is possible that further accumulation of clinical experience will provide answer to the question of the necessity and safety of flow-diverting stent installation in patients with such aneurysms.

Summary

Intravascular intervention, both alone and in combination with open surgery, is an effective treatment of VB aneurysms, whose clinical picture is manifested by brainstem compression symptoms. The use of flow-diverting stents allows achieving high radicalness in the long-term period in most cases without deterioration in the functional outcome. Treatment of fusiform aneurysms of the basilar artery trunk requires separate consideration and an individual approach due to a high risk of thrombosis of short branches feeding the brainstem.

Participation of authors:
Concept and design of the study — A.I., S.G., L.R.
Data collection and processing — S.G., A.P., G.B., E.V.
Text writing — S.G.
Editing — A.I.

Authors declare no conflict of interest.

REFERENCES

The article highlights hot issues in surgery of large and giant vertebrobasilar aneurysms. To date, open surgery for these aneurysms is associated with a high risk of complications and in most cases impossible. There have been attempts of using intravascular interventions for the treatment of this type of pathology in the history of endovascular neurosurgery. Despite low traumatic risk of such manipulations, the treatment results have been disappointing until recently: it constituted up to 50% of the lethal cases in deconstructive surgeries using a balloon catheter.

The situation has slightly changed with the appearance of microcoils and stent-assisted technique. However, adverse outcomes shifted from the early postoperative period to the long-term period due to recanalization and increase in aneurysm in size. To date, there are flow-diverting stents (FDS) available in the arsenal of endovascular surgeons, which allow redirecting the blood flow to the aneurysm-bearing vessel and creating conditions for thrombosing of the aneurysm cavity.

The team of authors presented the experience of the treatment of vertebrobasilar aneurysms accompanied by neurological disorders associated with brainstem compression in 8 patients. Fusiform and saccular aneurysms were diagnosed in an equal number of patients. The article is relevant, since it presents analysis of the first experience of applying different techniques of endovascular treatment in patients with a pathology that have been previously considered as incurable. FDSs were used in 5 cases, which allowed preservation of the aneurysm-bearing vessel lumen and thrombosing of the aneurysm cavity. It should be noted that no complications were observed in these patients. This technique is currently the method of choice for the treatment of large and giant aneurysms. However, a detailed study of the long-term results of the treatment is required for evaluation of its effectiveness.

Since the aim of the surgery for giant aneurysms, in addition to achieving occlusion of aneurysm from the bloodstream, is elimination of the compression of the posterior cranial fossa, the authors’ suggestion to perform decompressive trepanation of the posterior cranial fossa in cases of aggravated neurological symptoms associated with rapid aneurysm thrombosis in the early postoperative period deserved attention. Indications for this intervention should be clearly defined in the future.

It is not completely clear how the decision on which type of endovascular intervention to chose was made due to unspecified dimensions of the aneurysm. As for the large and giant aneurysms, it is unlikely that the use of microcoils, even in combination with stent assistance (in 2 patients), is an adequate method of treatment due to the impossibility to eliminate brainstem compression and high risk of recanalization and subsequent aneurysm growth. Indications for stenting in a patient with a fusiform aneurysm of the basilar artery, which resulted in the patient’s death, are not fully understood. If this was a case of dolichoectasia, the patient could be left under observation with recommendations for blood pressure stabilization and lifelong administration of disaggregants.

The authors conclude that this trend requires further development in order to work out the most optimal algorithm for patient selection and a clear definition of indications for different types of endovascular interventions for large and giant vertebrobasilar aneurysms, which is reasonable.

S.B. Yakovlev (Moscow, Russia)
Endoscope-Assisted Keyhole Approach in Cerebral Aneurysm Surgery

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1Russian Medical Academy of Continuing Professional Education, Moscow, Russia; 2Inozemtsev City Clinical Hospital, Moscow, Russia

The last decades in neurosurgery have been marked by the rapid development of minimally invasive techniques, including the use of the concept of keyhole/burrhole surgery and active introduction of endoscopic techniques. These alternatives to traditional approaches have minimized concomitant injury to tissues and the brain and improved functional and cosmetic outcomes. Endoscopic assistance in keyhole approaches, along with its use in traditional approaches, seems even more reasonable because the field of microscopic view is considerably limited in the case of a mini-approach.

Aim — we present our experience of using endoscopic assistance (EA) in aneurysm surgery through supraorbital and transorbital keyhole approaches.

Material and methods. We describe the surgical technique, indications for EA, and possible complications. In the period between 2014 and 2107, we used EA in the surgical treatment of 40 patients with cerebral aneurysms of the internal carotid (37 patients) and basilar (3) arteries. In all cases, 0 and 30° rigid endoscopes were used. The EA technique involved standard stages: assessment of anatomy before clipping and assessment after clipping. In 5 (12.5%) patients, clipping was performed under endoscopic visualization. The follow-up period was 6—12 months, on average.

Results. All patients underwent successful clipping of aneurysms without neurological complications. There was no death, disability, or serious permanent approach-associated complications in the study group.

Conclusion. EA is a safe and effective technique providing additional visualization in keyhole surgery of aneurysms.

Keywords: minimally invasive surgery, keyhole neurosurgery, endoscopic assistance, cerebral aneurysms.

Material and methods

In 2014—2017, we used EA in surgical treatment of 40 patients with cerebral aneurysms (10 patients in the late posthemorrhagic period and 30 patients with unruptured aneurysms). The distribution of aneurysms by location was as follows: 37 ICA aneurysms, including 25 aneurysms of the PComA orifice, 10 ophthalmic aneurysms, and 2 aneurysms in the AChA region (Table). All patients after SAH were in a compensated state, with treated CSF, and without clinical/angiographic manifestations of angiospasm. In 5 (12.5%) patients with ICA aneurysms, the disease onset manifested as oculomotor nerve paresis. The female : male ratio was 2:1. The mean age of patients was 54.9 years. All patients underwent native and 3D CT angiography. Preoperatively, patients were informed of alternative traditional surgical approaches. The surgical approach was chosen after a thorough evaluation of the anatomy of intracranial structures and aneurysms. The keyhole approach was performed only if analysis of the neuroimaging data suggested safe aneurysm obliteration. Most aneurysms were small or
medium in size, no more than 15 mm in diameter. In 3 cases, aneurysms reached 16—18 mm in diameter. One patient had a giant thrombosed supraclinoid ICA aneurysm. During follow-up, a complete neurological examination, including functional evaluation of the facial and frontal nerves, was performed. Satisfaction with cosmetic results was assessed using a 5-score scale: 1 — excellent, 2 — good, 3 — satisfactory, 4 — unsatisfactory, 5 — poor [11].

Surgical technique

The keyhole approach was performed according to a previously described technique [3, 4, 14]. The skin was incised along the eyebrow for SOC and MOZC and natural fold of the upper eyelid for TPC. The position and size of the frontal sinuses and supraorbital notch were obligatory considered, so the incision position was slightly varied depending on the individual skull shape. The decision of EA was made individually, with allowance for the intraoperative situation. Paraclinoid and supraclinoid ICA aneurysms and superior OA aneurysms were considered as indications for EA.

During the transorbital approach, particular attention was given to preservation of facial innervation and careful handling of tissues. The size of craniotomy was 2 to 3 cm. After dura opening, the traditional microsurgical技术 was used. Early brain relaxation was achieved by opening the arachnoid cisterns and dissecting the Sylvian fissure with visualization of the ICA up to the bifurcation and initial segments of the ACA and MCA. Adequate brain relaxation is extremely important not only for microsurgical manipulations but also for securing the routes of subsequent EA. In parallel, a further vector of dissection was determined. This depended on the aneurysm location and size.

The opticocarotid triangle and retrocarotid space were dissected as soon as possible. In the case of aneurysms in the PComA orifice region, any temporal lobe traction was excluded after hemorrhage. During dissection, the AChA was always verified, first under microscopy control. In 7 (18.9%) cases, extradural and intradural resection of the anterior clinoid process was performed. After performing standard microneurosurgical procedures and dissection of the aneurysm environment and arteries, preliminary evaluation was carried out using EA. Then, after clipping of the aneurysm, the clipping area was repeatedly explored using an endoscope (Fig. 1).

In surgery of superior OA aneurysms, the neuroanatomy and relationship between the aneurysm and the clinus and dorsum sellae are carefully evaluated. We used the minimally invasive approach only in the case of unruptured OA aneurysms. We used the mini-orbitozygomatic approach with an eyebrow incision. Of all the keyhole approaches, this is the most aggressive one; this access is an alternative to the classic fronto-orbitozygomatic approach. The aggressiveness is explained by the extent of resection of the skull base structures, which, on the one hand, makes the approach more traumatic, but, on the other hand, provides additional space for manipulations and significantly extends surgical corridors to the interpeduncular cistern structures. In addition to extradural resection of the anterior clinoid process, all patients underwent partial intradural resection of the posterior clinoid process.

The microsurgical technique in general does not differ from that of traditional approaches. After dissection of the opticocarotid and retrocarotid spaces, the possibility of manipulations in the interpeduncular cistern through these triangles is evaluated. EA plays an extremely important role in the case of a low OA bifurcation because a direct microsurgical field of view does not allow accurate evaluation of an individual topographic anatomical picture around the aneurysm. Preliminary EA enables planning of clip placement to the neck, and subsequent endoscopic control allows assessing the adequacy of clipping. One patient underwent coagulation and transection of the PComA for expanding the retrocarotid space. Preservation of perforating vessels branching from the PComA is critical; for this reason, resection is usually performed closer to the P1 segment of the PComA (Fig. 2). In more than half the cases, EA was supplemented with intraoperative fluorescent angiography.

Results

In all cases, EA enabled improved illumination of a deep and narrow wound, enhanced visualization of the perianeurysmal environment, and planning of vectors for effective and safe dissection of the aneurysm and perforating arteries. The use of 30° endoscopes significantly improved visualization through the opticocarotid and retrocarotid spaces both in the case of paraclinoid ICA aneurysms and in the interpeduncular cistern upon evaluation of superior OA aneurysms before and after clipping. There were no complications related to the use of EA in our group.

All aneurysms were completely excluded from the cerebral circulation, which was confirmed by both intraoperative opening of aneurysms followed by control with indocyanine green fluorescent angiography and control 3D SCT angiography in the postoperative period. Seven (17.5%) patients underwent correction of the clip posi-
Fig. 1. Clinical case 1.
Clipping of a left ICA aneurysm using endoscopic assistance.
a — planning of a skin incision along the natural fold of the upper eyelid on the left for transpalpebral tranorbital craniotomy; b — SCT angiography: a saccular supraclinoid ICA aneurysm (arrow); c — intraoperative view through a 0° endoscope after clipping of the aneurysm neck: 1 — ICA, 2 — oculomotor nerve; d — intraoperative view through a 30° endoscope after clipping of the aneurysm neck: 1 — ICA, 2 — anterior choroidal artery, 3 — A1 segment of the anterior cerebral artery, A — aneurysm; e — postoperative SCT angiography: the aneurysm is excluded from the blood stream; f — patient appearance 2 months after surgery.
Fig. 2. Case 2.
Clipping of a basilar artery aneurysm using endoscopic assistance.

a — SCT angiography: a saccular basilar artery bifurcation aneurysm; b — intraoperative view through a 0° endoscope: C — clivus, A — aneurysm, 1 — P1 segments of the posterior cerebral artery; c — intraoperative view through a 0° endoscope: a clip on the aneurysm neck is seen; the arrow indicates the orifice of a resected posterior communicating artery; d — postoperative SCT reconstruction; clips are seen in the basilar artery bifurcation area; e — SCT reconstruction of the skull: condition after orbitofrontal craniotomy of the skull on the right; there is a bone defect in the orbital roof area; the anterior clinoid process is resected.
tion due to perforator stenosis revealed by EA findings. There were no permanent approach-associated complications and deaths. There were also no intraoperative aneurysm ruptures.

The technical features of using EA in the case of small craniotomy and limited access include mandatory microscopic control during insertion and removal of an endoscope. In 5 (12.5%) cases of ICA aneurysms, bi-manual clipping was performed directly under endoscopic control. In this case, the endoscope was fixed to a pneumatic holder.

Postoperative complications were assessed at 2 weeks and 6 months. Periorbital edema of varying severity occurred in all patients and was not regarded as a complication because it completely regressed within 3 to 5 days after surgery. Temporal muscle atrophy in the approach area was present in 2 (5%) patients after MOZC. Oculomotor nerve paresis developed in 2 (5%) patients with OA aneurysms, which completely regressed within 2 months.

A postoperative cosmetic outcome at 3 and 6 months was assessed by patients as excellent and good. The best cosmetic outcome was achieved in patients after TPC because the incision was hidden in the natural fold of the upper eyelid. In a group of patients after SOC and MOZC, mainly good outcomes were obtained. There were no poor or unsatisfactory consequences. There was no alopecia in the eyebrow area.

Postoperative liquor rhoea occurred in 1 (4%) patient, which required placement of a lumbar drain for a period of 5 days.

Discussion

In recent years, aneurysm clipping has no longer held an absolutely leading position in surgery of cerebral aneurysms due to the development of endovascular techniques. However, the use of minimally invasive approaches, if it is safe and effective, reduces the number of approach-associated complications of clipping. First of all, concomitant injury to the brain is minimized in the setting of traction trauma. The concept of endoscope-assisted microsurgery was popularized by G. Fries and A. Perneczky [10]. In this case, the main advantage of EA is the ability to visualize “blind” zones beyond the microsurgical view. Direct and angular endoscopes are traditionally used for EA. Direct endoscopes enable enhanced visualization of important structures and improve illumination of necessary areas. Angular endoscopes provide information that can not be obtained with a microscope alone. The role of EA is especially important in assessment of perforating vessels when it is necessary to exclude their stenosis or occlusion during clipping [9—13]. Our experience, as well as the results of other authors [1, 3, 5, 8—15], indicates that aneurysm obliteration is possible in all patients if they are correctly selected. According to different authors [1, 10, 15—17], recliping due to arterial stenosis or inadequate aneurysm exclusion varies in a range of 7—20%. In our group, clip repositioning was required in 7 (17%) patients, mainly for control of the AChA. Intraoperative indocyanine green fluorescent angiography was used for additional control of perforating arteries and aneurysm exclusion [12, 18].

Regarding the technical aspects of EA application, it is necessary to note importance of the camera position for convenience of manipulations in limited space. The simplest choice is the orientation of upper camera part at the patient’s legs [12]. From a technical point of view, simultaneous microscopic control is necessary during EA upon insertion and removal of the endoscope. Caution of both the operator and the whole operating team is extremely important during EA. The neurosurgeon should not only be very experienced in vascular neurosurgery, both through traditional and through the keyhole approach, but also have technical skills for endoscopic manipulations.

Despite the obvious advantages, an endoscope may be a dangerous tool. According to some authors [16, 17], injury to the brain tissue and the risk of intraoperative aneurysm rupture are potential complications of EA. In our series of cases, there were no such complications. To prevent these complications, some authors have used a pneumatic endoscope holder.

We consider careful selection of patients as the main measure for prevention of complications in keyhole surgery using EA. Similarly, careful selection of candidates for minimally invasive surgery is also necessary. That is why minimally invasive techniques are more suitable for unruptured aneurysms or for compensated patients in the posthemorrhagic period. In our practice, we have not used EA in the acute period of hemorrhage upon any manifestations of brain edema and in patients in a decompensated state (Hunt-Hess grade III or IV).

Conclusion

Supraorbital and transorbital approaches, with properly selected patients, are effective and safe in aneurysm surgery. Disadvantages associated with mini-approaches, such as limited illumination and freedom for manipulations with microtools, may be eliminated by using endoscopic assistance, especially in patients with aneurysms of the internal carotid artery and upper segments of the basilar artery. Endoscopic assistance improves visualization and illumination of critical structures before and after clipping and enables evaluation of hidden structures beyond a direct microsurgical view.

Authors declare no conflict of interest.
In surgery of cerebral aneurysms, there are quite specific indications for endoscopic assistance. Most often, endoscopic assistance may be used for aneurysms of the internal carotid artery, basilar artery bifurcation, and intracranial segment of the vertebral artery, i.e. in cases of wide arachnoid cisterns and the possibility of inserting an endoscope. The main task solved by endoscopic assistance is identification of the position of clip jaws relative to the aneurysm neck and small perforating arteries. Is this control possible without an endoscope? Certainly yes! Intraoperative flowmetry and intraoperative angiography with indocyanine are most adequate for this purpose. Therefore, endoscopic assistance may be considered as an additional option.

Regarding super-small craniotomies in surgery of cerebral aneurysms, experts at the Burdenko Neurosurgical Institute adhere to the point of view that the need and reasonability of craniotomy size depend on the surgical challenges. The super-small size of craniotomy should not be an end in itself. In the case of intraoperative aneurysm rupture, craniotomy insufficient for manipulations in depth of the surgical wound may be fatal for the patient.

Regarding minimally invasive techniques for treatment of cerebral aneurysms, emphasis should be placed first of all on the endovascular technique. This technique is developed very fast and depends on technological innovations, each of which significantly extends the indications for application of this technique and improves surgical treatment outcomes.

Sh.Sh. Eliava (Moscow, Russia)
Surgical Treatment of Epilepsy in Patients with Mediobasal Temporal Cavernous Malformations


Objective — epilepsy is a frequent clinical manifestation of cavernous malformations (CMs) of the mediobasal temporal region (MBTR). Surgical removal of CMs is an excellent technique for treating associated epilepsy and may range from pure lesionectomy to tailored resection of the temporal lobe.

Purpose. The study purpose was to determine the optimal surgical management for epilepsy in patients with CMs of the MBTR.

Material and methods. We retrospectively analyzed the clinical data, neuroimaging findings, surgical techniques, and surgical outcomes in 11 patients with epilepsy and CMs of the MBTR. All patients underwent video-electroencephalography, magnetic resonance imaging, and computed tomography in the pre- and postoperative periods. Nine patients underwent preoperative implantation of foramen ovale electrodes. In all cases, surgery was accompanied by electrocorticography (ECoG).

Results. CMs were located in the anterior MBTR in 7 cases, anterior and middle thirds of the MBTR in 1 case, middle third in 2 cases, and middle and posterior thirds in 1 case. In 8 patients, preoperative monitoring revealed a seizure onset area in the MBTR. These patients underwent cavernomectomy with ECoG-guided resection of the hemosiderin ring and adjacent tissue using the pterional (4 cases) or supracerebellar transtentorial approach (4). In 3 cases, anterior temporal lobectomy with cavernomectomy was additionally used due to spreading of pathological activity to the lateral temporal neocortex. Seizure control after surgery was excellent in 7 patients (class 1 ILAE) and good in 4 (class 2 ILAE).

Conclusions. Surgery in patients with epilepsy caused by CMs of the MBTR should be performed based on non-invasive and invasive presurgical evaluation. If the seizure onset area is located in the MBTR, lesionectomy with ECoG-guided resection of the adjacent temporal cortical areas can be performed using the pterional or supracerebellar transtentorial approach. Lateral spread of epileptic activity requires cavernomectomy and anterior temporal lobectomy.

Keywords: epilepsy, cavernous malformation, temporal lobe, mediobasal temporal region, electrocorticography, supracerebellar transtentorial approach.

Abbreviations:
CM — cavernous malformation
CT — computed tomography
MRI — magnetic resonance imaging
MBTR — mediobasal temporal region
STA — supracerebellar transtentorial approach
ECoG — electrocorticography
EEG — electroencephalography

Supratentorial cavernous malformations (CMs) of the brain are often accompanied by epileptic seizures; in this case, the rate of intractable epilepsy significantly increases if the lesions are located in the temporal lobe. Asymptomatic microhemorrhages to the adjacent brain tissue, perifocal hemosiderosis, and gliosis are the leading pathogenic factors of epilepsy associated with CMs. The location of a CM in the mediobasal temporal region (MBTR), which is a derivative of the archicortex and periarchicortical area, occurs in 10—20% of cases and is associated with an increase in the number of medically refractory forms of epilepsy [1—10].

Microsurgical interventions not only eliminate the mass effect of a CM but also prevent inevitable intra- and perifocal hemorrhages specific for the natural course of cerebral CMs. The optimal strategy for treatment of CM-associated epilepsy has not been determined yet despite numerous studies on this topic. Studies have demonstrated that resection of a CM is significantly more effective in patients with a relatively mild epilepsy course. Rare temporary seizures disappear in 95% of cases after isolated resection of a CM; in patients with intractable forms of epilepsy, this surgical approach leads to only partial improvement in 50—73% of cases or has no effect at all.

The microsurgical treatment strategy involves mandatory resection of a CM, which is sometimes combined with resection of a perifocal gliotic hemosiderin rim or additional resection of the adjacent cerebral cortex under electrocorticography (ECoG) control. Extension of resection is based on the fact that an insufficient antiepileptic effect after isolated cavernomectomy is caused by the formation of a pathological epileptic system in the adjacent cortex. Applied “extended resections”, “temporal lobectomies”, and “anterior temporal lobectomies” are based on resection of the brain tissue adjacent to a CM and differ from each other only in the resection extent of anatomically intact structures. Comparative analysis of published outcomes is very difficult due to a significant
variety of used terminology, preoperative protocols, microsurgical techniques, and criteria for outcome evaluation in different studies [1—3, 11—23, 25, 26, 28—32].

The purpose of this work is to describe the tactics of surgical treatment of epilepsy associated with medial cavernous malformations of the temporal lobe and to assess the efficiency of used surgical techniques.

Material and methods

We performed a retrospective study of clinical, diagnostic, and surgical data of 11 patients (7 females and 4 males aged 16 to 48 years) (Table). The cases were selected based on two criteria: registered epileptic seizures and the presence of MBTR CMs confirmed by micro-morphological examination. All patients underwent a standard preoperative examination with assessment of the neurological status, semiology of seizures, their duration, frequency, and efficacy of anticonvulsant treatment. Patients underwent MRI and CT of the brain to assess the size, structure, and localization of MBTR CMs.

Video-electroencephalographic monitoring (video-EEG monitoring) to identify the source of pathological activity was carried out using a Cadwell computerized electroencephalography system. Recording was conducted using a 19-channel unipolar lead with separate ear electrodes. In 9 cases, invasive recording was used to clarify the location of a pathological activity source; for this purpose, platinum electrodes (Integra Lifesciences Corporation) were implanted in the medial or lateral temporal lobe, into the oval foramen on the CM side. Implantation was performed under fluoroscopic control and was not accompanied by complications.

EEG signals were processed using unipolar lead with paired ear electrodes. ECoG was performed using corticography arrays (Auragen Integra Lifesciences Corporation) with 20—48 electrodes for the lateral temporal lobe and strips with 6 electrodes for the medial temporal lobe.

All 11 patients underwent surgery under endotracheal anesthesia; the pterional approach was used in 7 cases; the paramedian access and supracerebellar transtentorial approach (STA) were used in 4 cases. During surgery, the length of resection of the temporal lobe structures adjacent to a CM was monitored using ECoG.

In the postoperative period, neurological complications as well as CT and MRI data were evaluated; patients continued anticonvulsant therapy prescribed on the basis of video-EEG monitoring and a seizure diary. The treatment outcome was assessed using the epilepsy surgical treatment outcome scale ILAE at 6 and 12 months.

Results

According to MRI of the brain, CMs were located in the anterior third (7 cases), anterior and middle thirds (1 case), middle third (2 cases), and middle and posterior thirds (1 case) of the MBTR. In all cases, CMs were located in the hippocampus and archipaleocortex (parahippocampal gyrus, uncus, and amygdala); in 2 patients, CMs additionally extended to the neocortical structures (fusiform gyrus) (Table). Neoplasms had a rounded shape with scalloped edges and a granular honeycomb structure as well as hemorrhages at different stages of hemoglobin transformation, typical of CMs. The size of CMs varied from 11 to 37 mm, and the thickness of hemosiderin rings surrounding CMs reached 2 mm. There was no contrast uptake, except for one case with slight uneven enhancement of the signal in a neoplasm.

In all patients, epileptic seizures developed focally, respectively to the CM localization. In 10 out of 11 patients, seizures were associated with impairment of consciousness, with focal non-motor onset being observed in 7 cases. Usually, seizures manifested by cognitive disorders with behavioral and emotional disturbances, followed by rapid transformation into bilateral tonic-clonic states. Focal motor onset seizures in the form of automatisms were present in 2 patients with CMs located in the anterior third of the MBTR (amygdala and hippocampal head). Focal non-motor autonomic seizures in the form of nausea and vomiting without impairment of consciousness were detected only in one patient with a CM of the left hippocampus body. The frequency of seizures ranged from 3 per month to 2 per day.

Three patients had single seizures that did not recur on anticonvulsant treatment (carbamazepine therapy in 1 case and valproic acid therapy in 2 cases). Among 3 patients with single seizures, a CM was located in the hippocampal head and body in 1 patient, hippocampal head and amygdala in the second patient, and hippocampal tail and fusiform gyrus in the third patient.

Preoperatively, 9 of 11 patients underwent anticonvulsant therapy mainly as carbamazepine or valproic acid monotherapy at medium therapeutic doses; in 1 case, combined finlepsin and toreal therapy was used. In 7 patients, the treatment had no effect on the frequency and severity of seizures.

The disease duration, from the first seizure to surgery, varied from 4 months to 15 years. The shortest disease duration was in 3 patients with single seizures; seizures did not recur on anticonvulsant treatment. In 8 cases, clinical data and video-EEG monitoring with simultaneous recording of electrical activity from foramen ovale electrodes indicated a leading role of the MBTR in onset of convulsive seizures, without initial involvement of the lateral temporal lobe cortex. In this subgroup of patients, the CM was removed through the pterional approach or paramedian STA with mandatory resection of not only hemosiderin-stained gliotic tissue but also intact brain tissue adjacent to the CM under ECoG control (Fig. 1). The following clinical case demonstrates removal of a MBTR CM without resection of lateral neocortical temporal structures.
Characterization of patients with epilepsy and MBTR CMs

<table>
<thead>
<tr>
<th>Age/gender/affectedside</th>
<th>Localization</th>
<th>Size, mm</th>
<th>Spread according to J. Schramm and A. Aliashkevich [35]</th>
<th>Approach</th>
<th>Surgery</th>
<th>Complication</th>
<th>Outcome (ILAE class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/M/L</td>
<td>AT—MT/HH, HB</td>
<td>20</td>
<td>A</td>
<td>PA</td>
<td>CE</td>
<td>Transient sensory aphasia</td>
<td>2</td>
</tr>
<tr>
<td>19/F/R</td>
<td>AT/HH, A</td>
<td>37</td>
<td>A</td>
<td>PA</td>
<td>CE</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>18/F/R</td>
<td>AT/HH, A</td>
<td>20</td>
<td>A</td>
<td>PA</td>
<td>CE</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>21/F/L</td>
<td>AT/HH, A</td>
<td>13</td>
<td>A</td>
<td>STA</td>
<td>CE</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>36/M/L</td>
<td>AT/HH, A</td>
<td>29</td>
<td>A</td>
<td>PA</td>
<td>CE</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>48/F/L</td>
<td>MT/HB—FG</td>
<td>14</td>
<td>?</td>
<td>PA</td>
<td>ATL</td>
<td>Transient sensory aphasia</td>
<td>2</td>
</tr>
<tr>
<td>29/F/R</td>
<td>AT/A—HH</td>
<td>22</td>
<td>A</td>
<td>PA</td>
<td>ATL</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>41/M/L</td>
<td>AT/HH, A</td>
<td>11</td>
<td>A</td>
<td>STA</td>
<td>CE</td>
<td>Transient fourth nerve palsy</td>
<td>1</td>
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<tr>
<td>29/F/R</td>
<td>PT—MT/HT—FG</td>
<td>26</td>
<td>?</td>
<td>STA</td>
<td>CE</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>25/M/L</td>
<td>MT/HH</td>
<td>15</td>
<td>A</td>
<td>STA</td>
<td>CE</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>41/M/L</td>
<td>AT/HH, A</td>
<td>15</td>
<td>A</td>
<td>PA</td>
<td>ATL</td>
<td>Transient sensory aphasia</td>
<td>1</td>
</tr>
</tbody>
</table>


Case 1

A 21-year-old female patient L. presented with complaints of periodic impaired consciousness episodes with tonic-clonic seizures, up to 2 to 3 times a day, not accompanied by aura. The episodes manifested at the age of 20 years. On treatment with Finlepsin at a dose of 200 mg/day, the frequency of episodes decreased to one per week. MRI of the brain revealed a MBTR CM located in the amygdala and left hippocampal head, 12×7×7 mm in size, with signs of previous hemorrhage (Fig. 2a). Neuropsychological testing revealed no speech, thinking, perception, memory, and praxis disorders.

Interictal scalp video-EEG monitoring revealed typical epileptic activity in the left posterofrontotemporal region, which was represented by the “spike-slow wave” complexes. To clarify the location and size of a pathological activity source, an electrode for an invasive video-EEG monitoring was implanted in the left oval foramen of the patient. Subsequent video-EEG monitoring for 2 days detected epileptic seizure with the ictal focus in the left medial temporal lobe region, without involvement of the lateral regions (Fig. 2b). Because the CM was located in the functionally important area of the speech dominant hemisphere, the paramedian STA was performed. After surgical exploration of the left medial temporal lobe, the CM surrounded by hemosiderin-impregnated brain tissue was detected in the anterior parts of the left hippocampus and amygdala (Fig. 2c). ECoG showed typical epileptiform activity in the altered cortical areas located 1 cm posterior to the cavernoma, which were resected together with the CM. The postoperative period proceeded without complications; the patient was discharged in a satisfactory condition without neurological deficit and seizures in the early postoperative period. Follow-up MRI of the brain 3 months after surgery revealed no residual CM tissue (Fig. 2d). At 12 and 24 months after surgical treatment, the patient condition corresponded to an ILAE class 1 outcome (no seizures and auras).

A preoperative examination revealed involvement of the neocortical temporal lobe structures in the generation of pathological activity in 3 patients. They underwent pterional craniotomy with removal of the CM and resection of anatomically intact anterolateral neocortical temporal structures (Fig. 3).

We present CM resection supplemented by anterior temporal lobectomy.

Case 2

A 48-year-old female patient K. was hospitalized with complaints of fainting episodes with convulsions as well as seizures without impaired consciousness, which were accompanied by a feeling of unreality, images of “previously unseen”, disorientation in the environment, and speech disorders. The frequency of generalized seizures reached one per month, with partial seizures occurring almost every day. The first seizure was accompanied by movement disorders in the right limbs and speech disturbances. The disease duration at the time of hospitalization was 7 years. The patient did not take prescribed anticonvulsant therapy.

CT and MRI of the brain revealed a CM of 14×12×10 mm in size in the MBTR on the left, which was located in the hippocampal body and fusiform gyrus (Fig. 4a).

Interictal video-EEG monitoring revealed epileptic activity in the left frontotemporal region, which was represented by “spike-slow wave” complexes without a clear
localization of the source, as well as regional slowing of activity in the right frontotemporal region.

The patient underwent implantation of electrodes into the oval foramina (Fig. 4b). Video-EEG monitoring detected “spike-slow wave” discharges with an amplitude of up to 120 µV in the left frontotemporal lobe, which did not spread to the left medial temporal lobe region; low-amplitude spikes (up to 40 µV) were detected simultaneously with a discharge under the left electrode in the oval foramen (Fig. 4c). There was no pathological activity on the right. Pterional craniotomy was used to place corticographic electrodes onto the lateral and basal polar parts of the left temporal lobe. ECoG revealed pathological activity in the left anterolateral temporal lobe, which required anterior temporal lobectomy and CM removal (Fig. 4d). In the early postoperative period, there was moderate sensory aphasia, which regressed on the 4th day. A follow-up examination at 12 months revealed an ILAE class 2 outcome (rare auras).

A micromorphological examination verified CMs in all patients. The anatomical results of surgery were assessed based on the MRI and CT findings at 7—10 days and 3—6 months. The findings showed that CMs were completely resected together with the surrounding hemosiderin-enriched brain tissue in all patients. In all patients, there was a communication between the perimesencephalic cistern and the temporal horn of the lateral ventricle, which was formed due to resection of the MBTR. In all cases of anteromedial temporal lobectomy, appropriate post-resection brain tissue defects were well visualized.

Postoperative neurological deficit was transitory and was mainly represented by moderate sensory aphasia in patients with CMs of the speech dominant hemisphere. Speech alterations developed in CM patients in whom the pterional approach to the MBTR was used; in this case, aphasic sensory disorders occurred in 2 patients.

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**Fig. 1. CM of the middle third of the MBTR; the paramedian STA.**

a — preoperative MRI scan, the CM is indicated by the arrow; b — postoperative MRI scan, the arrow denotes the resection cavity and a communication of the temporal horn with the perimesencephalic cistern; c — intraoperative image of the CM (marked with the asterisk); d — intraoperative image after CM removal, the temporal horn (TH) of the lateral ventricle is visualized.
after anterior temporal lobectomy and in 1 patient after cavernmectomy.

In 1 case, a patient who underwent cavernmectomy using the paramedian STA developed mild transient IV nerve palsy that regressed 2 weeks after surgery.

Assessment of seizure control at 6 and 12 months demonstrated good outcomes in both patient groups, with only 4 patients experiencing rare partial seizures during the follow-up period (ILAE class 2). Three patients from this group underwent cavernmectomy, and 1 patient underwent anterior temporal lobectomy combined with cavernmectomy. After surgical treatment, 7 patients achieved complete control of seizures (ILAE class 1).

**Discussion**

The location of CMs in the temporal lobes is characterized by a high rate of epilepsy that rather quickly transforms into an intractable form. The development of epileptic seizures is caused by brain injury due to repeated hemorrhages from a CM with deposition of hemosiderin and death of cellular structures and conductive pathways, which leads to changes in local nervous networks and formation of pathological excitability. Injury to the cerebral cortex caused by a CM or its surrounding hemosiderin ring is often combined with epilepsy because deposition of hemosiderin leads to transformation of the brain tissue adjacent to the CM and to formation of epileptogenic foci [1, 4, 8, 9, 13, 16, 19, 20, 22, 26]. A. Williamson and co-authors [34] demonstrated increased generation of prolonged and high-amplitude postsynaptic potentials in the setting of hyperexcited synaptic responses in the medial temporal lobe areas distant from CMs and tumors.

On the basis of analysis of neocortical CMs only, K. Menzler and co-workers [7] showed the lack of a relationship between the frequency of epilepsy and the lobar distribution of CMs. Also, the authors demonstrated

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**Fig. 2.** CM of the anterior third of the MBTR; the paramedian STA.

- a — preoperative MRI scan, the CM is indicated by the arrow; 
- b — EEG recording fragment, an electrode is placed into the oval foramen (SPH L), epileptic activity from the MBTR without spreading to the lateral neocortex; 
- c — intraoperative image of the CM; the left middle cerebral artery (MCA), posterior cerebral artery (PCA), and internal carotid artery (ICA) are seen; 
- d — postoperative MRI scan, the CM is indicated by the arrow.
a high correlation of epilepsy with CMs localized in the mesial temporal regions in the case of temporal lobe involvement.

The temporal lobe is the most heterogeneous structure in comparison with other regions of the cerebral mantle because the temporal cortex is represented not only by the neocortex but also (to a large extent) by the archicortex and paleocortex. The MBTRs are covered with the three-, four-, and five-layered cortex in contrast to the basolateral surface formed by the six-layered neocortex. On the basal surface, the archicortical structures are separated from the neocortex by the rhinal and collateral sulci; on the medial surface, they are separated by the choroidal fissure [7, 29]. Transition zones of anatomical transformation of the archicortex into a six-layered laminar structure are involved in functional connections with more complex intracortical structures in the neocortex. Archicortical structures of the MBTR are char-

Fig. 3. CM of the anterior third of the MBTR; anteromedial temporal lobectomy.
a — preoperative MRI scan, the CM is indicated by the arrow; b — intraoperative image of the CM (asterisk) of the anterior third of the MBTR, the internal carotid artery (ICA) and optic nerve (ON) are seen; c — postoperative MRI scan, the resection cavity is indicated by the arrow.

Fig. 4. CM of the middle third of the MBTR; anteromedial temporal lobectomy.
a — preoperative CT scan, the CM is indicated by the arrow; b — CT scan after implantation of electrodes into the oval foramen for invasive EEG monitoring; c — EEG recording fragment, electrodes are placed into the oval foramina (SPH L, SPH R); seizure onset area in the lateral temporal lobe with low-amplitude (up to 40 µV) spikes in the left electrode area of the oval foramen; d — postoperative CT scan.
acterized by a higher epileptogenic potential due to these specific anatomical and functional features that lead to neurophysiological instability [7, 29]. In our group of patients, injury to the archicortex (parahippocampal gyrus) and underlying hippocampus was present in all cases; in 2 cases, there was combined involvement of the archicortex and adjacent basomedial neocortical structures of the fusiform gyrus.

The main goal of preoperative examination of patients with temporal epilepsy is their allocation into subtypes based on involvement of the medial and lateral structures in onset of convulsive seizures. It is most reasonable to use several diagnostic approaches: clinical neurological evaluation, MRI, and video-EEG monitoring [4, 7—11, 14, 15, 20, 21, 24, 25, 33, 34]. P. Quarato and co-workers [26] analyzed seizure semiology, anatomical localization of temporal lobe lesions, and ictal EEG manifestations and identified the mesial and lateral clusters of symptoms characteristic of temporal epilepsy subtypes. “Mesial” symptoms include MRI signs of medial lesions, clinical symptoms in the form of rising epigastric aura (sometimes associated with other vegetative symptoms), early orolalimentary automatisms, and dystonia of the contralateral upper limb, as well as 5—9 Hz ictal discharges localized in the temporal lobe. “Lateral” symptoms are represented by a combination of lateral structural lesions of the temporal lobe, psychic aura, auditory or vestibular symptoms, staring without orolalimentary automatisms, and 2—5 Hz ictal discharges in the temporal region. Based on the identified subtypes, P. Quarato and co-workers [26] divided patients with temporal epilepsy into three groups: with a mesial, lateral, and mesiolateral type of the disease, for which a certain surgical treatment option was used — from removal of an anatomical lesion to extended anterior temporal lobectomy.

Our group included 8 mesial cases and 3 mesiolateral cases of temporal epilepsy, which was the reason to use various surgical techniques. In patients with mesial epilepsy, the CM and hemosiderin ring were removed, and abnormal brain tissue adjacent to the pathological neoplasm was resected based on the ECoG data; patients with mediolateral epilepsy underwent anterior temporal lobectomy.

CMs themselves can not be epileptogenic because they do not contain nerve cells. In this regard, surgical treatment of epilepsy accompanying these vascular anomalies is associated with resection of the brain tissue surrounding CMs. Resection of the hemosiderin ring surrounding a CM usually is not technically difficult and can always be performed during removal of the lesion from the mesial temporal structures. The need to remove, together with the CM, perifocal gliosis with the hemosiderin ring has been emphasized in many studies because this significantly reduces the frequency of seizures. For example, in a group of 49 patients with temporal CMs, J. Kivelev and co-authors [28] found that 40 patients had epileptic seizures; in this case, epilepsy was detected in 10 out of 13 patients with MBTR CMs. The authors’ surgical approach that included removal of CMs and additional resection of the hemosiderin ring only in functionally safe areas led to a good outcome of treatment for temporal epilepsy, which reached 90% (Engel class 1 or 2 outcome). Some publications have denied importance of preoperative mapping and resection of anatomically “intact” brain tissue adjacent to CMs because comparative evaluation of the antiepileptic effect of this method and simple removal of the CM and hemosiderin ring has not revealed statistically significant differences [1—3, 8—12, 17—19, 21—23, 25, 28].

By using ECoG, C. Ferrier and co-authors [16] demonstrated the formation of secondary epileptogenic areas in the mesial temporal cortex and their spontaneous transformation into hyperactive foci during prolonged epilepsy. H. Sugano and co-authors [32] noted that resection of brain tissue with ECoG signs of epileptic activity improved treatment outcomes. Therefore, identification of the limits for resection of anatomically normal tissue is very important to provide the greatest antiepileptic effect of surgery.

Some authors, based on their own experience, have recommended the use of extended resections, up to temporal lobectomy, to better control epilepsy, but the difference in efficacy between CM removal and CM removal combined with partial temporal lobe resection does not reach statistically significant values.

An unsatisfactory antiepileptic result after selective resection of temporal lobe CMs, which requires repeated surgery to improve the anticonvulsant effect, indicates the need for preoperative EEG mapping and ECoG to identify the area of seizure onset and spread of electrical activity to adjacent brain areas. Based on the results of this examination, the most appropriate variant of extended surgical intervention is chosen [16, 20, 30, 32]. The importance of invasive video-EEG monitoring in identification of the epileptic focus and its subsequent surgical resection has been confirmed by many researchers. Our experience has demonstrated the necessity of using ECoG because it not only detects the epileptic activity of cortical structures around CMs but also confirms the antiepileptic effect of resection of visually intact parts of the temporal lobe.

On the basis of examination of 61 patients with temporal lobe CMs and epilepsy, J. Van Gompel and co-workers [30] reported that intraoperative ECoG usually detected epileptic foci outside the CM borders, which required additional resection of brain tissue and was accompanied by better control of seizures. Similar results were demonstrated by Y. Shan and co-authors [23] in a group of 52 patients with epileptogenic temporal CMs located in the medial (19 patients) and neocortical (32 patients) parts of the temporal lobe who underwent resection of malformations without using ECoG (11 cases) and using intraoperative monitoring (41 cases). Evaluation of the postoperative outcomes revealed a significant superior-
ity of positive indicators (Engel class 1 or 2) in the group with ECoG-controlled additional resection of brain tissue in comparison with the group without using it (87.8% versus 54.5%) [23]. On the basis of this experience, the authors recommended anterior temporal lobectomy or resection of the medial temporal lobe (amygdalohippocampectomy) in the case of CMs located medial to the collateral sulcus.

F. Vale and co-authors [29] reported the surgical strategies and analysis of treatment outcomes in 34 patients with epilepsy and temporal lobe CMs. In 10 cases, CMs were located in the medial temporal regions and manifested by a characteristic clinical picture. In 9 out of 10 cases, surgery involved complete resection of CMs with the hemosiderin ring and was combined with standard amygdalohippocampectomy; in 1 patient, a CM in the posterior medial regions remained unrectsed. In 9 patients, a morphological examination revealed, in addition to CMs, medial temporal sclerosis, which was not previously detected by MRI. The outcomes in the group of patients with medial temporal CMs were as follows: Engel class 1 outcome — 9 and Engel class 3 or 4 in 1 patient [29].

D.N. Okishev and co-authors [3] summarized the experience of successful surgical treatment of epilepsy in 14 patients with temporal lobe CMs; in this case, cavernomas were located in the uncus (8 patients), hippocampus (3 patients), and temporal lobe pole (3 patients). In 12 cases, CM removal was supplemented by simultaneous resection of medial temporal structures; in 2 cases, the medial structures were resected after 1 year due to failure of antiepileptic cavernectomy. Resection of the medial parts of the temporal lobe was limited to selective amygdalohippocampectomy in 10 patients and to anterior temporal lobectomy in the remaining 4 cases.

W. Jun and co-authors [31] evaluated the outcomes of surgical treatment of epilepsy associated with hippocampal lesions in a group of 56 patients with histologically different lesions of the MBTR and emphasized that a good antiepileptic effect may be achieved with equal success (Engel class 1 outcome in 80—83% of cases) both upon removal of only a neoplasm with adjacent brain tissue and upon significant resection of the temporal lobe including medial structures. In our study, the outcomes of surgical treatment of epilepsy in patients with MBTR CMs demonstrated the need for resection of the lesion together with perifocal gliotic tissue. The amount of resection of temporal lobe structures adjacent to the CM should be determined by invasive monitoring of the cerebral cortex electrical activity, which evaluates the extent of resection of epileptic foci.

The choice of a surgical approach to MBTR CMs depends on many factors including evaluation of dimensions of the CM and its surrounding hemosiderin ring, analysis of topographic relationships with the Sylvian fissure, perimesencephalic cistern, and temporal horn of the lateral ventricle, as well as the exact localization of the lesion relative to the long (sagittal) hippocampal axis. Surgical treatment of hippocampal lesions is performed through several operative approaches that may be divided into anteroposterior (pterional transylvanian and transcisternal), lateral—subtemporal (transcortical transventricular), and posterior (occipital interhemispheric and STA). Each of these surgical approaches has its advantages and disadvantages that should be considered when choosing the technique for resection of a CM localized in the medial temporal structures [35—40].

J. Schramm and A. Aliashkevich [35] subdivided MBTR tumors into four types, each of which was represented by anterior and posterior variants, depending on the relation to the line passing through the widest part of the midbrain (lateral geniculate body level) and dividing the temporal lobe into anterior and posterior parts. Type A delineates lesions that are located in the hippocampal head and parahippocampal gyrus, amygdaloïd body, and uncinate gyrus and do not extend beyond the collateral sulcus and choroidal fissure. Type B lesions are located more laterally, in the fusiform gyrus, and do not extend into the inferior temporal gyrus. Type C includes lesions that combine type A and B location features; type D is a group of lesions that extend to the temporal cortex, temporal stem, insular lobe, and inner capsule. To remove type A lesions, the authors used the transsylvanian approach supplemented with resection of the anterior third of the temporal lobe; subtemporal and transcortical approaches were used for type B neoplasms. For removal of type C and D lesions, resection of the anterior two-thirds of the temporal lobe through subtemporal, transsylvian, and transcortical approaches was most often used. Neoplasms located in the posterior MBTR were usually resected through the subtemporal approach.

In our group, the CM localization corresponded to type A in 9 cases and type C in 2 cases. For their resection, we used the pterional transsylvian approach (7 cases) and STA (4 cases). Partial temporal lobectomy was performed in 3 cases; the remaining type A and C CMs were resected through the transsylvian approach and paramedian STA. The experience of STA use demonstrated not only a high efficiency in resection of tumors located in the posterior and middle thirds but also the possibility of resection of the anterior MBTR structures [36—40]. However, in the case of large CMs located in the anterior MBTR (hippocampal head and amygdala), preference should be given to pterional craniotomy with the transsylvian approach.

**Conclusion**

The choice of a surgical technique for treatment of epilepsy associated with mesial temporal CMs is based on neurological manifestations, video–EEG monitoring data, and the size and location of a vascular malformation. Inclusion of invasive transoval EEG registration in the preoperative examination plan facilitates more accurate
identification of the epileptic activity generation area in the MBTR. The presence of characteristic clinical symp-toms, corresponding EEG deviations (mesial and mesio-lateral types), and location of CMs in the MBTR enable choosing an appropriate surgical technique for treatment of epilepsy. All patients should undergo removal of the CM along with the hemosiderin ring and resection of adjacent brain tissue under ECoG control, which may be performed through both the peritonal approach and the paramedian STA. Detection of seizure activity foi

in the central and lateral temporal lobe in patients with MBTR CMs necessitates ECoG from lateral and basal neocortical structures that are exposed using the perito-nal approach enabling partial anteromedial temporal lobectomy for treatment of epilepsy. The good and excel-lent outcomes achieved in all patients of our series confirm a high efficiency of the tactics used for surgical treat-ment of epilepsy associated with MBTR CMs.

Authors declare no conflict of interest.
The article is devoted to choosing of the amount of surgical intervention for resection of cavernous malformations (CMs) of the medial temporal lobe, which are manifested by epileptic seizures. The topicality of this problem is unquestionable because epilepsy is the most frequent manifestation of hemispheric CMs, and epileptic associated with temporal lobe CMs is most intractable and tends to be pharmacoresistant.

Recently, the so-called antiepileptic interventions have been increasingly used for medial temporal CMs associated with severe epilepsy. Their spectrum is wide: from resection of altered perifocal brain substance to “classical” surgery in the form of anterior temporal lobectomy and/or amygdalohippocampectomy. As the authors rightly indicate, there have been no clear criteria for choosing a certain intervention.

The group of patients presented by the authors is small but fairly homogeneous. The preoperative examination was aimed at the most accurate identification of the ictal focus; for this purpose, invasive EEG from frontal and temporal electrodes was performed in 9 cases. Based on preoperative data, the authors preferred to perform “small” operations in the form of CM removal combined with excision of an altered perifocal brain area under ECoG control; only in 3 cases, surgery was extended to anterior temporal lobectomy based on EEG signs of mesial temporal lobe epilepsy. In this case, the issues of an optimal approach used during surgery are described in detail. A good ILAE class 1 or 2 outcome was achieved in all cases.

Therefore, the authors have demonstrated that preoperative examination and intraoperative ECoG reduce surgery to a “small” operation with resection of the CM and perifocal zone in most cases.

The work is of undoubted interest both for determining directions of further research and for considering the problems of epileptogenesis and outcomes of surgical treatment presented in the literature.

O.B. Belousova (Moscow, Russia)
Orbital Hemangiomas: Capabilities of Modern Neuroradiological Diagnostics

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**Objective** — to study the capabilities of modern CT and MRI methods in the diagnosis of orbital hemangiomas and to identify the characteristic features of these tumors with allowance for their hemodynamics based on quantitative evaluation by CT-perfusion.

**Material and methods.** In the period from 2010 to 2016, 14 patients with cavernous hemangioma (CH) and 2 patients with capillary hemangioma (CapH) of the orbit were examined. The age of CH patients varied from 17 to 67 years (median, 53 years); 8 females and 6 males. The age of CapH patients was 35 and 54 years. All patients underwent surgery with subsequent histological verification.

CT-perfusion was performed in 10 CH patients and 2 CapH patients according to a developed low-dose protocol (80 kV, 200 mAs, $t_{scan}=40$ s) with allowance for a target localizer (80 kV, 120 mAs) and at a maximum radiation dose of not more than 4.0 mZv.

Neoplasm microrcirculation was quantitatively assessed by calculating hemodynamic parameters: blood flow velocity (BFV), blood volume (BV), and mean transit time (MTT). MRI without and with contrast enhancement was performed in 11 CH patients and 2 CapH patients according to the ophthalmologic protocol (Signa GE, 3.0 T) accepted at the Institute: without contrast enhancement — T1, T2, and T2-FLAIR modes, T1 and T2 with a Fat Sat technique at a scan thickness of 3 mm, and DWI MRI; contrast enhancement — T1 (three projections) mode, including the Fat Sat technique. SWAN (n=2) and non-contrast MR perfusion ASL (n=3) were also used. Diffusion-weighted images (DWI) were processed with calculation of the apparent diffusion coefficient (ACD).

**Results.** In all CH patients, CT-perfusion revealed low perfusion parameters of blood flow: $\text{BFV}_{\text{CH}}=0.86\pm0.37$ mL/100 g, $\text{BFV}_{\text{CH}}=4.89\pm2.01$ mL/100 g/min with a high mean transit time $\text{MTT}_{\text{CH}}=10.13\pm3.05$ s compared to the same parameters of blood flow in the normal white matter: $\text{CBV}_{\text{NormWM}}=1.63\pm2.22$ mL/100 g, $\text{CBFV}_{\text{NormWM}}=9.72\pm3.13$ mL/100 g/min, and $\text{MTT}_{\text{NormWM}}=6.76\pm2.78$ s.

In CapH cases, significantly increased blood flow velocity and volume values and a low MTT value in the tumor were observed: $\text{BFV}_{\text{CapH}}=10.30\pm4.10$ mL/100 g, $\text{BFV}_{\text{CapH}}=119.72\pm53.13$ mL/100 g/min, and $\text{MTT}_{\text{CapH}}=4.35\pm1.79$ s.

In the case of orbital hemangiomas, optimal MRI modes were T1 and T2 with the Fat Sat technique, a scan thickness of 3 mm, and intravenous contrast enhancement. The revealed pattern of contrast agent accumulation by CH, initially in the central part and then in the periphery, may be a useful radiographic sign in the differential diagnosis with other orbital tumors.

**Conclusion.** Modern CT- and MRI-based diagnostics of orbital hemangiomas provides not only the exact location, size, and spread of the lesion but also reveals the characteristic structural features of these tumors, and the use of perfusion techniques visualizes hemodynamics of the tumors. CT-perfusion-based hemodynamic parameters of cavernous hemangiomas typical of this type of hemangiomas may be used in the differential diagnosis with other tumors of this location. The use of contrast enhancement and the Fat Sat technique with a scan thickness of not more than 3 mm is optimal for MRI diagnostics of orbital hemangiomas.

**Keywords:** orbit, cavernous hemangioma, capillary hemangioma, CT, CT-perfusion, MRI, differential diagnosis.

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In the diagnosis of orbital of neoplasms, neuroradiologists pay special attention to the topography of the lesion, its location within the orbit, involvement of the orbital walls, optic nerve and its sheath, the degree of blood supply and, of course, assessment of the presumptive histological type of the lesion. The latter is especially important to determine the tactics of treatment, but, as practice shows, it is the most challenging problem when establishing the final diagnosis.

Vascular neoplasms are the most common orbital diseases and account for 25% of all primary tumors located at this site [1]. Although cavernous hemangiomas are probably not true tumors, they are more common than all other benign orbital neoplasms in adults and account for 3—9% of all orbital tumors [2—5].

The term “cavernous hemangioma” is widely used both in clinical practice and in scientific publications, but many authors believe that the term “cavernous malformation” or “cavernous venous malformation” [6—11] is more appropriate one, as evidenced by the results of immunohistochemical studies, which show that they rather belong to malformations than to benign tumors [12]. In our study, we use the World Health Organization Classification of Tumors of Soft Tissue and Bone [13], which regards these neoplasms as benign vascular tumors, and therefore we use the term “cavernous hemangioma”.

According to clinical and morphological picture, hemangiomas are classified into cavernous, capillary (also known as simple, juvenile, hypertrophied), racemose, and lymphangiomatous [1].

We examined the x-ray characteristics of two histologically confirmed types of orbital hemangiomas, cavernous (CH), and capillary (CapH) types, which were diagnosed in our group of adult patients.

Cavernous hemangiomas of the orbit, as a rule, are detected during the second—seventh decade of life, and the peak incidence in observed during the fifth decade [1, 11]. CH are very rare in younger patients [14].

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About 60% of patients are females. Recent research suggests the influence of female sex hormones on the clinical course of CHs [15, 16].

Unlike cavernous hemangioma, CapH is an innate neoplasm and manifests at birth or within the first years of life. In the literature, CapHs in children are often regarded as infantile ones. According to A. Garner [17] and other authors, some CapH are prone to independent regression. Thus, according to C. Shields [18], tumor increases during the first 3—6 months of life, then it gradually decreases from the 12th to the 18th month and becomes 30% smaller by 3 years and 75—90% smaller by 7 years of age.

CapH of the orbit are extremely rare in adults. According to S. Schwartz et al. [19], CapH larger than 1 cm is an important predictor of vision loss in a half of cases and requires treatment, including surgical one. In the case of CH, surgical treatment is performed in approximately 50% of cases [20—24].

Ophthalmological examination of patients, which precedes neuroradiologic diagnosis, plays a special role in the diagnosis of the orbital hemangiomas.

Neuroradiologic studies with an extensive repertoire of computer tomography and magnetic resonance imaging techniques, including perfusion and diffusion methods, not only contribute to improvement of the diagnosis due to possible evaluation of tumor hemodynamics and histological type, but also facilitate preoperative planning [25—30].

This study was aimed at studying the capabilities of modern CT and MRI techniques when diagnosing two types of orbital hemangiomas, cavernous and capillary ones, identifying the characteristic features of these tumors with allowance for their hemodynamics based on quantitative evaluation using CT perfusion.

**Material and Methods**

A total of 14 patients (7 females and 6 males) with CH and 2 patients with CapH were examined in 2010—2016. The age of CH patients varied from 17 to 67 years (median, 53 years). We examined 2 patients with CapH aged 35 years and 54 years. Histological verification of lesions was carried out in all patients.

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X-ray contrast agent with iodine concentration of 350—370 mg/mL was injected into a cubital vein at a dose of 40 mL and rate of 4 mL/s using an automatic injector. Scanning at the level of the tumor node in the orbits enabled selecting the optimal zones for measurements of perfusion parameters in both the tumor and surrounding tissues. Perfusion maps were generated in off-line mode on the ADW 4.0 GE workstation (Perfusion II protocol). Microcirculation in the neoplasm was quantitatively assessed by calculating its hemodynamic parameters: blood flow velocity (BFV), volume (BV), and mean transit time (MTT).

Conventional contrast-enhanced and non-contrast-enhanced MRI was carried out using a specialized protocol on the high-field Signa (GE) 3.0T MR scanner in 11 CH patients and 2 CapH patients. Before contrasting: T1, T2, T2-FLAIR, Fat Sat T1 and T2 (slice thickness of 3 mm), and DWI MRI. In the case of insufficient visualization of the optic nerves, IDEAL modes (T1, T2) were used. With contrast enhancement: T1 in three projections, including Fat Sat technique (3 mm). MR protocol was supplemented with SWAN mode (n=2) in order to identify the areas of micro-hemorrhage. In 2 CapH patients, non-contrast-enhanced MR perfusion was performed using ASL-technique (Arterial Spin Labeling) to determine blood flow in the tumor. Three CH patients were examined before surgery in other medical institutions using standard protocols.

**Results**

All patients had unilateral lesion of the orbit: left-sided lesion was observed in 6 cases and right-sided lesion was observed in 8 cases. There was intraorbital intraconal space-occupying mass in the internal surgical space in CH 9 patients, intraorbital extracanal — in 2 patients, and intraorbital tumor invading the medial portion of the middle cranial fossa through the upper orbital fissure — in 3 patients. In the cases with CapH, the tumor occupied the entire orbit and extraorbital tumor growth was observed.

Exophthalmos was observed in all patients. Visual dysfunction was observed only in patients with optic nerve compression at the apex of the orbit or in the visual canal; in the latter case, the descending partial atrophy of the optic disk developed. In 4 patients with compression at the apex of the orbit, signs of optic disc edema were observed during ophthalmoscopy. Oculomotor disorders and diplopia were observed in 12 patients. They were caused by compression of the muscular complex at the apex of the orbit in 9 patients, involvement of the nerves at the level of the superior orbital fissure and in the cavernous sinus — in 3 patients. In 7 cases, CHs were asymptomatic for a long time. In 1 patient with extraorbital CapH invasion into the paranasal sinuses and the base of the anterior cranial fossa, olfactory dysfunction was observed.
Separation of the tumor from the surrounding tissues of the orbit due to the presence of a “pseudocapsule” was a distinctive histological feature of CH. Histological picture of CH was represented by closely spaced extended vascular cavities lined with a single layer of flattened endothelial cells. Uneven wall thickness due to dystrophic changes in the form of fibrosis, hyalinosis, and deposits of calcium salts was observed. Macroscopic examination showed fibrous “pseudocapsule” surrounding the lesion, which shaped it into a well-delimited knot.

Microscopic pattern of CapH was represented by a pronounced lobular structure, but the capsule was absent as opposed to CH. There were the foci of proliferating endothelial cells and capillaries with fuzzy boundaries.

The results of histological studies of CH and CapH are shown in Fig. 1. Endothelial markers CD34 and CD31 are the main immunohistochemical markers for both histological types.

**Computed tomography**

CT images of CH were represented by rounded or oval well-delimited structures localized mainly at the area funnel of the orbit. The size of detected hemangiomas varied from 2 to 6 cm: it was less than 2 cm in 3 cases, 2—4 cm in 8 cases, and 4—6 cm in 3 cases. CapHs were quite large in both our cases, 4—6 cm. Large CHs had a pronounced lobular structure with a visible “pseudocapsule” and sometimes with compression of adjacent structures (intraorbital muscles and nerves) and caused local destruction of the orbital walls due to prolonged compression. X-ray density of CHs was characterized by homogeneous space-occupying masses isodense to the orbital muscles, 3 (21%) patients had hyperdense fragments due to microcalcinates. According to CT, the density of these structures was within the range from 37 to 57 HU, increasing by an average of 16.7 HU with intravenous contrasting (Fig. 2).

On CT, CapHs were visualized as moderately hyperdense structures without a clear capsule (Fig. 3). In our studies, both cases of CapH demonstrated intracranial growth of the tumor into the sellar area and the parasanal sinuses.

**CT perfusion**

Ten CH patients and two CapH patients underwent CT perfusion study with quantitative assessment of blood flow in these tumors, which showed low values of the mean perfusion parameters of blood flow in CHs: 
\[ \text{BF CH} = 4.89 \pm 2.01 \left( \text{mL} / 100 \text{ g} \right), \]
\[ \text{BF CH} = 10.30 \pm 4.10 \left( \text{mL} / 100 \text{ g} / \text{min} \right). \]

The plots reflecting the absolute values of CT perfusion parameters in CH vs those in the normal white matter: 
\[ \text{BF CH} = 0.86 \pm 0.37 \left( \text{mL} / 100 \text{ g} / \text{min} \right), \]
\[ \text{BF CH} = 1.63 \pm 0.37 \left( \text{mL} / 100 \text{ g} / \text{min} \right). \]

As can be seen from the plots, hemodynamic parameters of perfusion blood flow are reduced in CH. Thus, CT perfusion study showed a general pattern in the entire group of CH patients: low blood flow velocity and volume in combination with prolonged mean transit time in all CHs.

For the cases of CapH, we cannot draw conclusions because of the small number of patients in the group (n=2) and further data collection is planned.

**Magnetic Resonance Imaging**

In all 14 cases, CHs were homogeneous and isointense in T1-weighted images. In 9 cases, “pseudo capsule” clearly delineated the lesion due to the hypointense MR signal along the periphery, CH was characterized by hyperintense T2-weighted MR signal. Internal septums were visible in lesions larger than 2 cm in diameter (n=11). Contrast enhancement of MR images was heterogeneous and mild.

In the first series of contrast-enhanced MR images, mostly central part of CH was contrasted; later on, in the subsequent series (dynamic contrasting), contrast agent was also distributed along the periphery (Fig. 8). In our opinion, this feature of the contrast agent accumulation by CH is quite specific for these lesions and can be useful in differential diagnosis. Contrasting of the structure of large CH may be mild and heterogeneous.

In our opinion, contrast-enhanced MRI with suppression of the MR signal from fat (Fat Sat) is the optimal technique for visualization of orbital hemangiomas.
The study should be carried out in thin slices (no more than 3 mm) (Fig. 9).

Capillary orbital hemangiomas were characterized by non-homogenous MR signal in standard modes T1, T2, T2-FLAIR. The tumors intensively accumulated contrast agent. Micro-hemorrhages were well traceable in the form of multiple hypointense sites when using the SWAN mode. In both cases of CapH, non-contrast-enhanced MR perfusion (ASL) showed significant increase in blood flow velocity in the neoplasm, \( B \text{FCapH} = 237.0 \pm 17.58 \) (mL/100 g/min), compared to that in the white matter of the brain (\( \text{CBF}_{\text{NormWM}} = 20.0 \pm 2.57 \) (mL/100 g/min.) This increase in blood flow velocity in CapH was the reason for additional use of 3DTOF MR-angiography, which demonstrated the presence of a fine-mesh vascular network in the projection of the funnel of the orbit with blood supply from the ophthalmic artery. This vascular network was only visualized at the base of the tumor and did not involve its entire volume (Fig. 10), which exactly matched hyperperfusion sited in ASL-BF maps. In the case of CapH, apparent diffusion coefficient (ADC) was increased (\( \text{ADC}_{\text{CapH}} = 0.00113 \)) compared to that of normal white matter (\( \text{ADC}_{\text{NormWM}} = 0.00084 \)).

Radiological characteristics of CH based on CT and MRI studies, including quantitative assessment of the blood flow in these tumors by CT perfusion, are summarized in the Table.

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**Fig. 1.** Histological preparations.

Cavernous hemangioma (a). Hematoxylin and eosin staining, x100 magnification. Capillary hemangioma (b). Staining with endothelial marker SE34, x200 magnification.

**Fig. 2.** Cavernous hemangioma of the orbit. Different patients.

a — CT in the axial projection on the right shows a lobular space-occupying mass with small cysts. The tumor invades the funnel of the orbit; deviation of the medial wall of the orbit is observed; b — CT of the intraconal space-occupying mass on the right that intensively accumulates contrast agent and causes medial dislocation of the optic nerve; c — CT in the axial projection demonstrates a large tumor of the orbit with a large petrificate at the anterior pole, causing exophthalmos and excavating orbital walls.
### Radiological characteristics of CHs based on CT, CT perfusion, and MRI

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age, years</th>
<th>Lesion location</th>
<th>CT density (HU) after CE</th>
<th>Bone destruction</th>
<th>CT perfusion</th>
<th>MRI</th>
<th>Contrast enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>36</td>
<td>Intraconal</td>
<td>52</td>
<td>No</td>
<td>5.22±1.89</td>
<td>11.0±2.24</td>
<td>Isointens</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>51</td>
<td>Extracanal</td>
<td>49</td>
<td>No</td>
<td>Not applied</td>
<td>Isointens</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>48</td>
<td>Intraconal</td>
<td>37</td>
<td>No</td>
<td>3.61±1.11</td>
<td>13.6±2.32</td>
<td>Hypointens</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>55</td>
<td>Extracanal</td>
<td>53</td>
<td>Yes</td>
<td>10.09±0.34</td>
<td>9.21±2.89</td>
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</tr>
<tr>
<td>5</td>
<td>F</td>
<td>60</td>
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<td>42</td>
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<td>13.01±3.89</td>
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<tr>
<td>6</td>
<td>F</td>
<td>54</td>
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<td>Not applied</td>
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<td>F</td>
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<td>No</td>
<td>Not applied</td>
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<td>Slightly hyperintens</td>
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<td>9</td>
<td>M</td>
<td>58</td>
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<td>57</td>
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<td>1.26±0.21</td>
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</tr>
<tr>
<td>10</td>
<td>M</td>
<td>48</td>
<td>Extracanal</td>
<td>51</td>
<td>No</td>
<td>4.17±2.75</td>
<td>5.27±1.86</td>
<td>Intense</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>52</td>
<td>Extracanal</td>
<td>39</td>
<td>No</td>
<td>3.41±1.45</td>
<td>8.36±3.33</td>
<td>Not applied</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>64</td>
<td>Intraconal</td>
<td>44</td>
<td>Yes</td>
<td>5.43±1.12</td>
<td>11.2±2.99</td>
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</tr>
<tr>
<td>13</td>
<td>M</td>
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<td>Intraconal</td>
<td>42</td>
<td>No</td>
<td>3.92±0.88</td>
<td>12.31±3.0</td>
<td>Slightly hyperintens</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>50</td>
<td>Intraconal</td>
<td>39</td>
<td>No</td>
<td>4.52±1.41</td>
<td>12.0±2.54</td>
<td>Inhomogeneous, intense</td>
</tr>
</tbody>
</table>

**Footnote.** * — the values of perfusion parameters in normal white matter of the brain are given in parentheses.
Fig. 3. Capillary hemangioma of the right orbit.
Axial contrast-enhanced CT shows a large tumor of the right orbit invading the sphenoid bone, cells of the ethmoidal labyrinth and even bulging into the funnel of the right orbit. Intensive contrasting of the tumor is observed.

Discussion

There is no consensus in the literature on terminology and classification of hemangiomas, which can lead to confusion, inadequate diagnosis and tactics of treatment. Thus, according to A. Hassanein et al. [32], the term “hemangioma” was incorrectly used in 228 (71.3%) of 320 analyzed publications. According to J. Mulliken and J. Glowacki [33], the term “hemangioma” is more appropriate for true neoplasms with vascular cavities formed due to proliferation of endothelial cells of the capillary network. The authors believe that hemangiomas are biologically heterogeneous: in some hemangiomas, endothelial cells demonstrate pronounced proliferative activity, and on this basis they can be classified as vascular tumors, while in other hemangiomas, proliferative activity of endothelium is absent and they are considered as developmental defects [33, 34].

Fig. 4. Cavernous hemangiomas of the orbit. Different patients.
a — small CH with characteristic low blood flow velocity BF (d); b — large CH of the right orbit with characteristic low blood flow volume in the neoplasm (e); c — CH of the left orbit with prolonged MTT in the tumor (f).
Fig. 5. Cavernous hemangioma of the right orbit.
Axial CT scan (a) shows an intracranial tumor of the right orbit that accumulated contrast agent in its central portion. CT perfusion maps (b–d) show low hemodynamic values in most of the tumor (b — CBF, c — SBV) and prolonged MTT (d); blood flow is increased in the central part of the tumor (the site matching the most intensely contrasted area).

Fig. 6. Plots of the absolute values of CT perfusion parameters in CH (red) and normal white matter (WM) of the brain (blue).
a — blood flow volume BV (mL/100 g); b — linear blood flow velocity BF (mL/100 g/min); c — mean transit time MTT (s).
According to the revised and modified classification of the International Society for the Study of Vascular Anomalies (ISSVA, 2014), based on the concept of J. Mulliken and J. Glowacki [7], vascular anomalies are classified into vascular tumors and vascular malformations: capillary hemangioma is considered as benign vascular tumor regardless of its capability of involution. Cavernous hemangioma is considered as “cavernous venous low-velocity malformation” [6, 10, 35]. Earlier classifications of orbital tumors (for example, AFIP Atlas of tumor pathology, 2006) distinguish capillary and cavernous hemangiomas [36].

Degradation processed accompanied by formation of new cavities that are included in the total blood flow take place in CH nodes. These processes can take decades. Hemodynamic changes, revascularization processes, and formation of extensive foci of mucoid dystrophy in the stroma can lead to significant increase in CH size. A. Garner [17] attribute CH growth to endothelial hyperplasia, which causes ischemia followed by microthrombosis. G. Harris and F. Jakobiec [37] attribute increase in CH to capillary proliferation accompanied by formation of cavernous cavities due to progressive ectasia. According to W. Míller-Forell and E. Boltshauser, thrombotic sites may occur in CH [38] due to slowed blood flow in

![Fig. 7. Plots of perfusion blood flow parameters in CH normalized to white matter values (nBV, nBF, nMTT).](image)

![Fig. 8. Large cavernous hemangioma of the right orbit.](image)

Contrast-enhanced (c—e) and non-contrast enhanced T1-weighted (b) and T2-weighted (a) axial MRI demonstrate multilobular structure of the tumor, heterogeneously accumulating contrast agent. Frontal MRI shows pronounced accumulation of contrast medium along the periphery.
**Fig. 9. Cavernous hemangioma of the right orbit.**
Fat Sat T1-weighted MRI in the axial projection (a, b) and frontal reformation (c) shows heterogeneous accumulation of contrast medium by the central part of the tumor, which then spreads over the entire volume of the neoplasm.

**Fig. 10. Disseminated cranoorbital capillary hemangioma. Continued growth.**
Contrast-enhanced T1-weighted axial MRI (a) shows a tumor of the right orbit with proliferation into the sellar area and nasal passages, intensively accumulating the contrast agent. Multiple small foci of hemorrhage can be observed in the tumor in SWAN mode (b), which results in speckled pattern. High blood flow velocity is clearly visible in the tumor in ASL mode (c) $\text{BF}_{\text{CapH}} = 237.0 \pm 7.58$ (mL/100 g/min) compared to blood flow velocity in normal white matter of the brain ($\text{CBF}_{\text{NormWM}} = 20.0 \pm 2.57$ (mL/100 g/min)). $d, e$ — diffusion coefficient is increased in the tumor: $\text{ADC}_{\text{CapH}} = 0.00113$ (ADC$_{\text{NormWM}} = 0.00084$). 3DTOF MRA (f) shows the vascular network of the tumor from the ophthalmic artery.
quite large cavernous cavities. CHs are typically not prone to hemorrhages and rupture of pseudocapsule, possibly because the structure of these lesions is rich in the fibrous tissue. Let us keep in mind that in our study, hemorrhages were detected only in the CapH group.

When classifying hemangiomas, it should be noted that most childhood hemangiomas are capillary from the histological viewpoint, since they are represented by immature capillary masses. CapH is very rare in adults. Thus, only 3 cases were found in publications of A. Reese [39]. A.F. Brovkina [1] reports cases of 5 patients aged 12 to 23 years (1 child, 3 males, 1 female). Other authors [40—43] report rare cases of CapH in adult patients. In our material covering a 5-year period, two histologically verified cases of CapH of the orbit were found. A. Stagner and F. Jakobiec [44] proposed CapH classification based on the studies of these neoplasms in children and adults and identified histopathological features of CapH in both age categories, as well as differences in the clinical course and immunohistochemical staining. When analyzing the variants of CapH, the authors noted similar lobular structure of infantile hemangiomas in children and CapH in adults, which are GLUT-1 negative and non-involuting over time.

The use of perfusion CT in our study revealed characteristic hemodynamic changes in the structure of CH, thereby increasing specificity of differential diagnosis and accuracy of tumor boundaries. This statement can be exemplified by our observations of patients with CH and optic nerve glioma (Fig. 11). Note that the first studies of orbital tumors based on CT perfusion were carried out at the Burdenko Neurosurgical Institute (V. Kornienko, I. Pronin et al., 2005 [45]).

We found no similar studies on the use of perfusion CT in the diagnosis of the orbital hemangiomas (Medline, search depth up to 2017).

Differences in MRI characteristics of CapH and CH tissue and accumulation of contrast agent are due to the structural features of these neoplasms. Intensive accumulation of contrast medium by CapH is attributed to the presence of a rich capillary network in the tumor. In our opinion, accumulation of contrast medium from the central part to periphery characteristic of CH, which is observed during dynamic contrasting, is highly important in MRI studies and enables differentiating these orbital.

![Fig. 11. Cavernous hemangioma of the orbit (upper row). CT (a) and CT perfusion (b, c). Low hemodynamic parameters of velocity (b) and volume (c) in the cavernous hemangioma. Glioma of the optic nerve (lower raw). CT (d) and CT perfusion (e, f). Perfusion values of velocity (e) and volume (f) are moderately increased in glioma.](image-url)
tumors from other tumors located at this site. Many authors emphasize that the use of dynamic MR imaging plays a decisive role in the differential diagnosis of orbital hemangiomas, neurinomas, and other tumors [46–49].

**Conclusion**

Wide variety of orbital lesions and diseases and differences in their biological nature necessitate the development of new approaches and techniques in differential diagnosis. Modern diagnosis of orbital hemangiomas using CT and MRI determines not only the exact location, size, spread of the lesion, but also shows characteristic structural and hemodynamical features of these tumors. Low hemodynamic parameters of cavernous orbital hemangiomas, which are characteristic of this type of hemangiomas, determined using CT perfusion can be used in a differential diagnosis with other tumors located at this site.

The use of contrast-enhanced Fat Sat technique with a slice thickness of no more than 3 mm is optimal for MR diagnostics of orbital hemangiomas.

**Authors declare no conflict of interest.**

**REFERENCES**

Mass lesions of the orbital structures were always associated with certain diagnostic difficulties. Hemangiomas are not the most common lesions of the orbit, but they account for up to 80% of vascular orbital tumors. In this paper, the authors focus on two types of hemangiomas, cavernous and capillary ones, in adult patients, which is of great interest from the viewpoint of morphology of these tumors, their hemodynamics, and diagnostic techniques. The article presents macro- and microstructure of these tumors and characteristic features of both types. CT and MR protocols suggested by the authors provide complete diagnostic information required to determine the tactics of surgical treatment, and the use of novel techniques (CT perfusion, SWAN and ASL MRI) provides high accuracy of the differential diagnosis. The authors found that quantitative evaluation of hemangioma hemodynamics based on the CT perfusion is the key element in the differential diagnosis of cavernous hemangiomas of the orbit. In CT studies of orbital lesions, special attention is paid to the problem of reducing the radiation exposure of patients. The authors proposed protocols based on reduced technical parameters of the tomographic scanner (X-ray tube parameters: 80 kV, 120 mAs) and 80 kV, 250 mAs for CT perfusion; the total radiation exposure was no more than 4 mSv per patient. The authors present a detailed modern diagnostic set of methods for radiodiagnosis of the orbital hemangiomas, but the study could be supplemented with a more detailed picture of differential diagnosis, for example, with such neoplasms of the orbit as meningiomas, gliomas, pseudotumorous lesions, and metastases.

**Commentary**

Mass lesions of the orbital structures were always associated with certain diagnostic difficulties. Hemangiomas are not the most common lesions of the orbit, but they account for up to 80% of vascular orbital tumors. In this paper, the authors focus on two types of hemangiomas, cavernous and capillary ones, in adult patients, which is of great interest from the viewpoint of morphology of these tumors, their hemodynamics, and diagnostic techniques. The article presents macro- and microstructure of these tumors and characteristic features of both types. CT and MR protocols suggested by the authors provide complete diagnostic information required to determine the tactics of surgical treatment, and the use of novel techniques (CT perfusion, SWAN and ASL MRI) provides high accuracy of the differential diagnosis. The authors found that quantitative evaluation of hemangioma hemodynamics based on the CT perfusion is the key element in the differential diagnosis of cavernous hemangiomas of the orbit. In CT studies of orbital lesions, special attention is paid to the problem of reducing the radiation exposure of patients. The authors proposed protocols based on reduced technical parameters of the tomographic scanner (X-ray tube parameters: 80 kV, 120 mAs) and 80 kV, 250 mAs for CT perfusion; the total radiation exposure was no more than 4 mSv per patient. The authors present a detailed modern diagnostic set of methods for radiodiagnosis of the orbital hemangiomas, but the study could be supplemented with a more detailed picture of differential diagnosis, for example, with such neoplasms of the orbit as meningiomas, gliomas, pseudotumorous lesions, and metastases.

*M.B. Dolgushin (Moscow, Russia)*
**Introduction**

Facial pain has been described since the days of Aretaeus, a physician and philosopher of the ancient Roman Empire. Since then, advances in its diagnosis and treatment have made it possible to achieve partial control over them. However, such types as deafferentation and neuropathic facial pain (LB), which are characterized by extreme resistance to pharmacological treatment, remain the subject of research.

Deafferentative pain (DP) is defined as a strong spontaneous pain with a decrease or complete absence of perception of sensitive stimuli [1]. The clinical picture of this condition is characterized by loss or change in facial sensitivity in the form of allodynia, hyperalgesia or dysesthesia in the pain area.

A common cause of facial DP is denervation of the trigeminal nerve [2]. This condition also occurs in damaged thalamus and V nuclei in the brainstem and upper spinal cord. Both the surface and deep types of sensitivity (including somatosensory) are involved in the formation of the deafferentation pain impulse, the primary motor area is also involved but indirectly [1]. The appearance of pain is assumed to be associated with reorganization of the motor and sensory cortical areas (which correspond to the deafferented body part) accompanied by expansion of central representation area in the cerebral cortex. The mechanism of DP development has not been fully studied yet and is supposedly associated with the cessation of afferent impulse transmission to the cerebral neurons, which is accompanied by impaired inhibitory effect and increased neuronal excitability. In other words, representation of the body part in the cortex undergoes changes, and this part of the cortex does not consider the lost part to be missing and replace the remaining received impulses with pain. Pathophysiological mechanisms of deafferentation, probably, include impaired release of neurotransmitters by nerve cell endings [3, 4]. Pain matrix is formed in addition to psychological and emotional factors.

The delayed development of DP after destructive procedures is associated with plastic changes in the brain [1]. A. May [5] suggested that the cortical and subcortical morphological changes diagnosed in patients suffering from various types of chronic pain can be regarded as secondary changes resulting from constant pain. Chronic pain is accompanied by structural and functional changes in the nervous system, changes in the chemical mechanisms of brain activity (called inadequate neuronal plasticity), which leads not to disease compensation, as in other medical conditions, but to impaired brain function [6].

The question regarding the optimal type of treatment for DP is still open. Motor cortex stimulation (MCS) was originally used to treat thalamic pain. T. Tsubokawa et al. [7] published an experience of using MCS in 11 patients with thalamic pain in 1991. A number of modern studies demonstrate positive effect of MCS in central neuropathic pain.
The current study presents the results of treatment of poorly controlled facial pain in 8 patients using MCS as well as an analysis of the literature on this issue.

**Material and methods**

The study included 8 patients (3 males and 5 females) who were implanted with a system of constant motor cortex stimulation at the Illinois University in Chicago in 2004—2016 and Novosibirsk Federal Center of Neurosurgery in 2017. The patients’ age ranged from 37 to 81 years (mean age, 57.5 years). Burchiel classification (2003) and the international classification of headache disorders, 3rd edition (2013) were used for identification of FP types.

Neuropathic facial pain served as indication for surgery: deafferentation trigeminal pain was observed in 5 patients, deafferentation pain combined with glossopharyngeal neuralgia (GN) was diagnosed in 1 patient; post-stroke pain (PSP) in the facial area in 2 patients was caused by a stroke in the thalamus and in the medulla oblongata (Fig. 1).

Characterization of patients, including etiological factors of facial pain development, are presented in Table 1.

The average duration of pain syndrome prior to intervention was 9 years (minimum, 1 year; maximum, 16 years).

Scale-based assessment of the pain severity was performed at admission to hospital, at discharge, and during follow-up. The visual analogue pain scale and Barrow Neurological Institute pain scale (BNIPS) were used. All patients upon admission complained of a constant burning pain that did not stop after administration of various drugs (5 points according to the BNIPS scale). The intensity of pain by VAS at admission varied from 8 to 10 points (the average value was 9.3 points).

Decreased facial sensitivity was assessed by the patients according to Barrow Neurological Institute facial hypoesthesia scale (BNI fhs) (2000) [8]. Severe numbness and anesthesia (3—4 points of the BNI fhs scale) were observed in 6 patients prior to surgery. No sensitivity disorders were diagnosed in the patient with GN.

For test stimulation, which was carried out in 6 patients for 5—7 days, epidural electrodes were installed after craniotomy. The effect in the form of a decrease in pain intensity by 50—80% was obtained upon test stimulation. The system of constant motor cortex stimulation was installed immediately in two patients.

For all patients, electrodes for constant stimulation were implanted into the epidural space and located perpendicularly or longitudinally relative to the central sulcus (Fig. 2).

A neuronavigation system was used during intervention for defining localization of the facial area and positioning of the electrodes on the cerebral cortex based on preoperative standard and functional MRI data (obtained during contraction of the facial muscles, tongue and jaw movements) (Fig. 3).

After craniotomy, somatosensory potentials were recorded to identify the central sulcus, motor and sensory cortex (Fig. 4).

Next, monopolar epidural stimulation of the cortex was performed to localize the areas responsible for the movement of the arm and facial muscles. Positioning of the electrodes on the cortex was carried out based on the results of test stimulation at which the motor response from the facial muscles was obtained. Eight- or 16-contact electrodes were used for stimulation.

Postoperative complications were classified using the scale by F. Ibanez et al. [9], which has 4 gradations and takes into account both systemic and specific neurosurgical complications.

We managed to obtain information on the course of disease for all patients after discharge. The follow-up period after intervention was from 3 to 48 months (an average of 10.6 months).

Patients evaluated treatment efficiency using 0—100% scale at discharge and during follow-up period. According to the M. McLaughlin scale [10], 75 to 100% pain relief was considered as a “very good” surgery outcome, 25 to 75% pain relief was considered as “good” outcome, and less than 25% pain relief was considered as “unsatisfactory” outcome.

**Results**

A significant improvement in the form of pain relief by 80—100% was noted in 4 patients immediately after intervention. Pain intensity decreased by an average of 67.5% at discharge according to the patients’ evaluation (table 2).

No systemic disorders and deterioration of the neurological status were observed in patients in the postoperative period. Subcutaneous hematoma in the generator area was diagnosed in 1 case after surgery, which was then punctured. Thus, the severity of complications after MCS was no more than 2a grade according to the scale by F. Ibanez et al.

One patient sought medical attention on the 4th day after discharge with complaints of the “crooked face” and speech disturbance after stimulation; changes in stimulation parameters allowed eliminating the adverse outcomes.

Infectious complications were noted in 1 case. The patient was readmitted to hospital with intracranial infection and postoperative scar erosion after 3 months. The stimulation system was removed and then reinstalled 5 months later. The stimulation was successful in both interventions, with almost complete relief of pain.

Pain syndrome in the follow-up decreased by 55% in total. MCS effectiveness was assessed by patients as very good according to the McLaughlin scale in 3 cases, as good in 4 cases and unsatisfactory in 1 case. The inter-
Fig. 1. Medulla oblongata stroke accompanied by Wallenberg-Zakharchenko syndrome in a 53-year old patient.
T1-image of the brain in the axial (a) and sagittal (b) projections. Lesion area is indicated by an arrow.

Table 1. Characteristics of patients with MCS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease duration, years</th>
<th>Type of facial pain</th>
<th>Etiology</th>
<th>Surgical interventions preceding MSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 years, female</td>
<td>5</td>
<td>DP</td>
<td>Damaged TNR in MVD (?)</td>
<td>MVD of the TNR in 2001</td>
</tr>
<tr>
<td>56 years, female</td>
<td>14</td>
<td>DP</td>
<td>Multiple destructive interventions on TNR</td>
<td>Absent</td>
</tr>
<tr>
<td>65 years, male</td>
<td>1</td>
<td>PSP</td>
<td>Thalamic ischemic stroke in 2004</td>
<td>AICA aneurysm clipping in 1993, trigeminal ganglion compression, MVD, two RFD, neuroectomy of the trigeminal nerve</td>
</tr>
<tr>
<td>37 years, female</td>
<td>15</td>
<td>DP</td>
<td>Repeated surgical interventions on TNR and in the facial area</td>
<td>Two MVD, infraorbital nerve blocks, two surgeries on the maxillary sinus cavity and tendon of the superficial masticatory muscle, TMJ arthrocentesis</td>
</tr>
<tr>
<td>81 years, female</td>
<td>14</td>
<td>DP</td>
<td>Destructive intervention on the trigeminal nerve</td>
<td>Neurotomy for TN, supraorbital PNS, implantation of MCS in 2005, replacement of MCS generator in 2009 and 2011</td>
</tr>
<tr>
<td>53 years, female</td>
<td>6</td>
<td>DPFF</td>
<td>Multiple destructive interventions on the GNR</td>
<td>IX nerve MVD in 2013, IX and X nerve rhizotomy, gamma knife in 2013, percutaneous nucleotracototomy under SCT in 2014</td>
</tr>
<tr>
<td>53 years, male</td>
<td>1</td>
<td>GN</td>
<td>Ischemic stroke of VBS in 2015, Wallenberg-Zakharchenko syndrome</td>
<td>MCS in June 2016, removed due to infection after 3 months (Sept. 2016), reinstallation in Nov. 2016</td>
</tr>
<tr>
<td>48 years, male</td>
<td>16</td>
<td>DP</td>
<td>Multiple surgical interventions on TNR and in the facial area</td>
<td>Removal of the maxillary sinus cysts in 2001, alcoholization of the trigeminal ganglion in 2016</td>
</tr>
</tbody>
</table>


vention resulted in almost no pain relief in 1 patient: according to the patient, the pain decreased by no more than 5—10% in the period of 2 months.

Discussion

Neuroanatomical aspects of MCS

There are many assumptions concerning the mechanism of MCS. However, it remains unclear. Recent research findings, functional MRI and positron emission tomography data provide some suggestions for understanding MCS effectiveness:

1. Pain and counterpain stimuli from the thalamus are regulated at the cortical level under normal conditions. In case of lost inhibitory mechanism, MCS suppresses pain impulses via stimulation of the pathways from the motor cortex to the thalamus that reduce hyperactivity in the networks associated with the thalamic pain pathways [11, 12]. T. Tsubokawa et al. [7] found that MCS suppresses hyperactivity of low-threshold thalamic...
neurons while stimulation of the sensory cortex did not show such effect.

2. An increase in blood flow in the ipsilateral thalamus, brainstem, cingulate gyrus, anterior islet, and orbitofrontal cortex is observed in patients who respond well to MCS [13].

3. The emotional component is also affected by activation of the production of endogenous opioids in various brain structures [14].

4. MCS is assumed to restore the control of the antinociceptive system over the nociceptive system not only at the cortical level [14]. R. Pagano et al. [15] and R. Chiou et al. [16] propose hypotheses on a decreased inhibition of neurons of the periaqueductal gray matter and suppression of nociceptive impulses from the spinal cord.

5. Activation of GABAergic interneurons and descending inhibitory pathways at the brainstem and cortical levels, activation of functional neural networks in stimulation areas are increased [17, 18].

6. Successful MCS in patients after stroke presumably leads to increased glucose metabolism in the ipsilateral thalamus [19].

7. Disrupted processing of the nerve impulse due to the added noisy input to the current activity is also possible [20].

8. Psychological factors such as expectation of analgesia based on the patients’ beliefs and desires also influence positive response to the treatment of neuropathic pain [21].

Features of the MCS method

Surgical technique and stimulation parameters vary significantly between different studies; MCS method was corrected by the researchers with time. To date, there is no standard for electrode application: perpendicular or parallel, subdural or epidural options exist. According to
C. Honey et al. [22], there are significant differences in the surgical technique between the surgical centers where such interventions are performed, these differences may influence the outcome. X. Zhang et al. [23] showed the absence of significant differences in the effectiveness of treatment outcomes between the use of epidural and subdural electrodes and recommend epidural positioning of electrodes in order to prevent their displacement or development of subdural accumulation of CSF. K. Hosomi et al. [24] achieved a quicker analgesic effect during test stimulation with subdural installation of electrodes between the primary motor cortex and the primary sensory cortex. However, the effect decreased with chronic stimulation. Nevertheless, despite various technical nuances, one can achieve positive results of stimulation.

Many authors [25, 26] emphasize that positioning of the electrode over the motor cortex corresponding to the painful part of the body should be as accurate as possible. This can be achieved in subdural location of the electrodes.

According to the results of modern studies, the effect of brain stimulation depends on the electromagnetic properties of the tissue, which reacts differently to different stimulation methods. Apparently, this fact requires the precise positioning of the stimulating electrode in order to achieve the highest therapeutic efficacy [24, 27, 28]. A. O’Brien et al. [27] emphasized the need to specify the topography of the altered brain tissue in patients with central post-stroke pain. Anatomical changes and accumulation of the CSF can affect the location, orientation and magnitude of the current near the site of lesion.

The question still remains unclear whether the precise positioning of the electrode is necessary or a change in the current amplitude/application of the electrode on the cerebral cortex responsible for a certain anatomical region is sufficient. After all, many authors note a good analgesic effect of stimulation in cases of unideal electrode positioning or severe brain atrophy, which can be also observed in phantom pains when direct stimulation of the zone of interest is impossible and electrode is to be positioned near the probable motor zones.

Test stimulation

According to many researchers, the efficacy of test epidural stimulation prior to implantation of a constant pulse generator is a criterion for the selection of patients for MCS [23]. However, the question concerning its necessity, as well as its replacement with test transcranial magnetic stimulation (TMS), is actively discussed in the literature.

Some authors note an increased risk of infectious complications during the test period, which is performed after craniotomy and installation of test electrodes in the epidural space and lasts up to 5—7 days. According to the literature [27, 29—31], infectious complications in MCS can constitute 2.2—5.7%, their frequency rate can be higher during test period (up to 22%). In this connection, some authors suggest immediate implantation of the system without test stimulation. According to A. Raslan et al. [32] who did not observe any infectious complications during a two-week stimulation, the risk of infectious complications can be minimized in case of a relatively short duration of the test period, qualitative wound care and separation of the stages of test and continuous epidural stimulation. There were no intracranial infectious complications in any of our patients who underwent the test stage.

**MCS efficacy**

Analysis of the literature showed a wide spread in the efficacy of chronic stimulation of the motor cortex in a group of patients with different types of FP (table 3).

According to the summarized literature data [23], there is no correlation between MCS outcomes and the origin, localization and type of FP, patients’ age and gender, as well as the type of stroke (thalamic/non-thalamic, ischemic/hemorrhagic) that caused FP. No dependence of MCS efficiency on various factors was also noted in our small patient setting. However, C. Honey et al. suggest that the pathogenesis of pain is important for effective cortical stimulation [22].

Furthermore, C. Nuti et al. [36] suggested that pain intensity during the first month after implantation of permanent electrodes is an important efficacy indicator. In general, our data show insignificant pain relief in case of ineffective stimulation after installation of the electrodes for chronic stimulation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>% of pain relief after surgery/during follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 years, female</td>
<td>Damaged TNR in MVD (?)</td>
<td>100/100</td>
</tr>
<tr>
<td>56 years, female</td>
<td>Multiple destructive interventions on TNR</td>
<td>60/40</td>
</tr>
<tr>
<td>65 years, male</td>
<td>Thalamic ischemic stroke in 2004</td>
<td>20/50</td>
</tr>
<tr>
<td>37 years, female</td>
<td>Repeated surgical interventions on TNR and in the facial area</td>
<td>80/80</td>
</tr>
<tr>
<td>81 years, female</td>
<td>Destructive intervention on the trigeminal nerve</td>
<td>80/30—60</td>
</tr>
<tr>
<td>53 years, female</td>
<td>Multiple destructive interventions on the GNR</td>
<td>10/5</td>
</tr>
<tr>
<td>53 years, male</td>
<td>Ischemic stroke of VBS in 2015, Wallenberg-Zakharchenko syndrome</td>
<td>80/80</td>
</tr>
<tr>
<td>48 years, male</td>
<td>Multiple surgical interventions on TNR and in the facial area</td>
<td>10/20—40</td>
</tr>
</tbody>
</table>
**Assessment of efficiency**

There is no stated agreement between the researchers in assessing MCS results and their criteria. C. Honey et al. [22] speculate about what percentage of the decrease in the initial pain should be regarded as a good outcome. For instance, pain relief by 25% may seem ineffective for a doctor, while it is significant for a patient [22]. In most studies, the criterion of MCS efficacy is still considered to be a 30 to 50% reduction in pain of the level of pain intensity upon admission by the VAS scale. Perhaps, indirect signs of MCS efficacy and improved life quality such as weight gain in debilitated patients or decrease in the dose or number of analgesic and antiepileptic drugs, vocational rehabilitation, and etc. should be also taken into account.

**Long-term results of MCS**

The antinociceptive effect of MCS can occur within a period of several days to several weeks after surgery. Apparently, this is due to not only a direct inhibitory signal from the primary motor cortex but also indirect pain relief through various antinociceptive systems [37].

A slight decrease in the MCS effectiveness over time is described in a number of patients [7, 38, 39]. The authors emphasize that the rate of a decrease in efficiency is one of the most important criteria. The sudden disappearance of the anesthetic effect of stimulation is often associated with electrode migration, technical problems or battery discharge.

One of the reasons for the gradual decrease in MCS efficacy is the reaction of the dura mater. F. Velasco et al. [40] described a case of a decrease in the MCS effect in connection with pronounced fibrosis at the site of electrode localization, which was accompanied by an increase in impedance of more than 2000 ohms. It is possible that surgical revision and meningolysis or subdural displacement of the electrode is required in cases of a decrease in stimulation efficacy.

The gradual loss of stimulation efficiency over time can be associated with the effect of the acquired tolerance to stimulation [41]. The authors [38, 42, 43] indicate the importance of parameter correction: some efforts are required to be made in order to change the settings prior to obtaining an effect before considering the stimulation ineffective. In some patients, change of the constant mode to cyclic, increase or shortening of the cycles of the “on” and “off” periods and other changes in stimulation settings restored the initial MCS efficacy. P. Slotty et al. [44] demonstrated that a 10% change in the stimulation parameters (current, impulse length, and frequency) can significantly enhance pain relieving effect. In our study, 3 patients sought for medical help in some period after discharge with complaints of a decreased stimulation efficacy. A more significant improvement was achieved after changing the generator settings or the program itself (from 20 to 40—50% of the pain relief efficacy). In 1 patient, MCS efficacy started decreasing immediately after surgery on a daily basis in the evening. Automatic change in current parameters during the day allowed achieving a uniform pain relieving effect.

**Predictors of successful stimulation**

The questing regarding the selection of suitable candidates for MCS remains open due to the variable clinical efficacy of MCS and its low efficacy in some of the cases [33, 45]. What types of facial pain should be treated with this method? What are the predictors of successful motor cortex stimulation? What patient groups should be selected for this type of treatment for the therapeutic efficacy to increase?

Many works are devoted to the identification of predictors of effective MCS in multiple TMS. Presumably, high-frequency TMS, like MCS, activates antinociceptive regions at the thalamic and spinal levels [14, 46]. Recent studies [47] have shown that the TMS effect has a 90% positive predictive value, while the absence of an effect has 40% of the negative predictive value. In order to exclude the false-positive effect of TMS, the authors recommend alternating stimulation with its imitation (placebo effect). X. Zhang et al. [23] showed a clear relation between preoperative TMS and MCS results. Good pain relief can be expected in patients with a positive response to TMS. The authors did not recommend using MCS in patients with no response to TMS. Our patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of FP, origin</th>
<th>Number of examinations</th>
<th>Follow-up/Mean follow-up</th>
<th>Pain relief during follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Kolodziej et al., 2015 [33]</td>
<td>PSP, DP, TNP</td>
<td>20</td>
<td>6 months to 6 years</td>
<td>75</td>
</tr>
<tr>
<td>H. Ebel et al., 1996 [34]</td>
<td>DP, PHN</td>
<td>7</td>
<td>5 months to 2 years</td>
<td>57</td>
</tr>
<tr>
<td>R. Buchanan et al., 2014 [35]</td>
<td>DP</td>
<td>3</td>
<td>3 months</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>PSP</td>
<td>2</td>
<td>3 months</td>
<td>26</td>
</tr>
<tr>
<td>A. Raslan et al., 2011 [32]</td>
<td>Different types of TNP in the facial area (FP after interventions on TNR and facial area, trauma, in Wallenberg syndrome, and etc.)</td>
<td>8</td>
<td>33 months</td>
<td>62</td>
</tr>
<tr>
<td>X. Zhang et al., 2017 [23]</td>
<td>PSP</td>
<td>16</td>
<td>28.2 months</td>
<td>40</td>
</tr>
<tr>
<td>Our data</td>
<td>DP, PSP</td>
<td>7</td>
<td>10.6 months</td>
<td>53</td>
</tr>
</tbody>
</table>
did not undergo TMS prior to intervention, so evaluation of a correlation between its effect and the results of the frontal cortex stimulation was not possible.

**Future directions of research**

To date, there are numerous studies promising more effective stimulation. For instance, stimulants with feedback, which can be activated during the occurrence of a pain attack or different periods of the day, taking into account the “sleep-wake” cycle, have been proposed. The design of new types of electrodes with a closer location of contacts can also increase stimulation efficacy [12].

Modern studies of the intracerebral pathways of the trigeminal nerve system lead to the new data on the physiology of pain. D. Henssen et al. [48] suggested that it is not only the contralateral but also ipsilateral trigeminothalamic pathway from the dorsal regions of the sensory nucleus of the trigeminal nerve to the cerebral cortex that are involved in facial pain formation. Ambilateral activation of the sensory cortex, medial dorsal nuclei of the thalamus, insular cortex, anterior cortex and precentral regions have been reported after painful stimulation in animals [48, 49]. Considering this data, it is possible that MRI and DTI studies can specify areas in which brain activation is the most sensitive in facial pain, suitable for stimulation and can be selected for MCS. Specification of the trigeminalthalamic and internuclear pathways involved in the pain system can improve MCS efficacy in patients with facial pain.

PET and functional MRI allowed identification of the involvement of the anterior insular cortex in pain perception [49]. The authors suggested that the insular cortex has its own pain modulation effect, while MCS demonstrates an additional modulatory effect. These results can initiate further studies on the identification of the brain areas to be subjected to the analgesic effect and can be introduced into practical neurosurgery.

Careful selection of patients and further search for predictors of the method efficacy are required for the use of MCS in chronic pain [8, 11, 39]. Apparently, it is impossible to perform a general analysis of the treatment outcomes in a group of patients that includes various types of pain, since, for example, deafferentation and post-traumatic pain have different pathogenesis [22]. Any expensive method of treatment for neuropathic pain should be based on selection of patients who can achieve a stable analgesic effect.

One of the main aspects of treatment efficacy is the importance of patient’s expectations from the intervention, as well as psychological and social factors, including the adaptive abilities of an individual and the tendency to pain catastrophizing, which plays an important role in the development and maintenance of chronic neuropathic pain syndromes [6, 41]. The future clinical trials of different methods will face the task of a personified approach in the treatment of neuropathic pain.

**Conclusion**

Deafferentation pain is a bothersome and poorly controlled condition. Recent studies and our results show that stimulation of the motor cortex may be one of the effective options for treating deafferentation facial pain. However, no precise criteria for selecting patients for this type of treatment have been identified yet. Even a slight decrease in the intensity of excruciating and debilitating pain, which patients evaluate as a good effect, gives grounds for the use of MCS in patients with FP. Additional studies that will help to identify the place of MCS in the world of pain syndromes in the facial area are required in order to determine the indications for this intervention and predictors of effective stimulation of the cerebral cortex.

**Participation of authors:**

Text writing, data collection and processing, statistical processing of the data — G.I. Moysak, D.A. Rzaev, V.M. Dzhafarov

Study design — D.A. Rzaev, K.V. Slavin

Data collection and processing — V.M. Dzhafarov

Concept and editing — K.V. Slavin

Authors declare no conflict of interest.

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3. Abram SE, Haddox JD. Any expensive method of treatment for neuropathic pain should be based on selection of patients who can achieve a stable analgesic effect.


Treatment of central pain is the most difficult task in pain surgery. As a rule, these are deafferentation pains, which are extremely difficult to tolerate by patients and, in many cases, cannot be treated by either conservative or surgical methods. The method of chronic stimulation of the central cortex appeared in the arsenal of pain surgery about 20 years ago [1], which gave hope for more effective control of these severe pains. More than a thousand publications have been accumulated during this period. According to the world literature [2], the effectiveness of MCS in the treatment of central pain syndromes varies within 40—65% (pain relief by 50% or more). Most authors [3] emphasize that stimulation of the central cortex is most effective in the treatment of facial pain. An interesting fact is that the etiology of facial pain is not always important [4]. In our own observations, we almost always received a positive response to the ES of the motor cortex in facial pain regardless of the location of two electrodes perpendicular to the central gyrus (in case of using four-contact electrodes). The use of electrodes with a larger number of contacts increases the potential of the ES and, may increase method effectiveness.

To date, there is still no unambiguous opinion on the need of a test period. Many researchers believe [5] that there is no need for a test period once positive results of transcranial magnetic stimulation (TMS) are obtained, and implantation can be performed immediately. This is justified by the fact that the effect of chronic MCS does not arise in most cases immediately, and prolongation of the test period up to a month and more is associated with the risk of infectious complications. It should be noted that, if not mentioning rare cases of false positive TMS results, false negative results, on the contrary, are found quite often. Therefore, we consider the test period to be mandatory in case if TMS has no effect. Moreover, there is always an option of conducting placebo ES in the test period (due to the lack of paresthesias in this type of stimulation). Unfortunately, the authors did not indicate whether they used this option or not and how its results correlated with the results of chronic ES.

As for the implantation technique, I would like to note that subdural positioning of the electrodes, despite how effective it is, can hardly be considered as the main option due to the high risk of postoperative liquorreha and infectious complications. Subdural arrangement of the electrodes can be considered as an alternative only in difficult-to-access cases, for example, if pain in the leg predominates in the thalamic pain, and if central representation of the leg cannot be found on the conventional surface (during intraoperative ES). In such cases, we prefer a more invasive DBS technique but at the same time avoid opening the dura mater.

It should also be noted that, despite dispersed opinions, the location of two electrodes perpendicular to the central groove in relation to the pain area is considered to be the most effective. Two front contacts are located on the motor cortex (cathodes) and two (anodes) are positioned on the postcentral gyrus (in case of using four-contact electrodes). The use of electrodes with a larger number of contacts increases the potential of the ES and, may increase method effectiveness.

When discussing the factors that affect the efficacy of motor cortex stimulation, it should be noted that psychological factors, and, in particular, severity of the psychogenic component in the complex picture of the pain syndrome, play not one of the many, but the primary role, as well as any other method of neurostimulation. This is noted by most authors [6, 7] and does not downplay the importance of the effect itself as if equating it to that for placebo. Even in case of a good effect (reliably confirmed by scales and tests), patients with a pronounced psychogenic component and severely suffering patients will still be dissatisfied with the results of the treatment that have not reached the level of their expectations. In the concluding part of this article, the authors also point out the importance of expectations, adaptive abilities of a person and pain catastrophizing, which play a major role in the development and maintenance of chronic neuropathic pain [8]. The “somatized” patients have many psychological problems that only exacerbate pain severity and create a vicious circle of “anxiety — pain — anxiety,” which cannot be torn by any of the methods without a serious psychotherapeutic effect.

Having analyzed the results of this study, I would like to note that, in several cases, the method of motor cortex stimulation was preceded by destructive interventions such as open rhizotomy and nucleotracotomy. In my opinion, and according to the data available to date on the role of destructive interventions in the development of deafferentation, it is difficult to predict the results of MCS if it precedes the destruction.

I would particularly like to emphasize the authors’ opinion on the evaluation of treatment outcomes. Indeed, regression of pain intensity by VAS is not one of the most important factor in improving the quality of life. Reduced amount of administered drugs, improved sleep quality, improved daily activity and other
parameters, which should be assessed using the scale of the quality of life, are much more important.

The most valuable part of this article is its conclusion: “Even a slight decrease in the intensity of excruciating and debilitating pain, which patients evaluate as a good effect, gives grounds for the use of MCS.”

In our country, this method has been used since 2003 first at Burdenko Neurosurgical Institute, then at Tyumen Federal Center of Neurosurgery and Novosibirsk Federal Center of Neurosurgery. We can only sincerely rejoice for the results obtained by the authors and the spread of this technique, which allows patients with the most severe pain syndromes to reduce their pain and suffering.

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REFERENCES

Implantation of VPS in The Early Postoperative Period Following Removal of Posterior Cranial Fossa Tumors in Children

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Burdenko Neurosurgical Institute, Moscow, Russia

PCF tumors are the most common tumors of the central nervous system in children. One of the main manifestations of these tumors is the development of hydrocephalus, the symptoms of which are in most cases the reason for the examination and diagnosis [1, 2]. Manifestations of hydrocephalus are resolved in most cases after tumor resection. However, the so-called persistent hydrocephalus remains in some patients and requires additional surgeries. According to the literature data [3—9], the need for shunt surgery after PCF tumor resection appears in 18—40% of cases among children (see table). These data were obtained by foreign authors based on the treatment results for children as far back as the 90s and are still cited in all of the modern studies [2, 10—16]. However, some qualitative changes occurred in neurosurgery over the past 20 years: surgeries became less traumatic, new imaging technologies appeared, the number of complications and hospitalization period decreased.

Given the altered situation in surgical practice, we decided to perform a modern research and evaluate the modern risk of persistent hydrocephalus development in children after PCF tumor resection, as well as to study the factors contributing to its formation.

Material and methods

Retrospective analysis included 155 children with PCF tumors without previously performed CSF shunt surgery who were operated on at Burdenko Neurosurgical Institute in the period of 2012 to 2014. Surgeries were performed by one surgeon according to a relatively standardized surgical technique. The aim of the surgery was complete tumor resection. There were no patients with partial or subtotal tumor resection in the study group. Complete removal of CSF occlusion and recovery of the CSF flow were observed in all cases by the time the surgery had been completed. In this regard, persistent hydrocephalus was considered by us as communicating hydrocephalus.

Criteria for determining the need for VPB implantation in the early postoperative period were the following: progressive ventriculomegaly with increasing neurological deficit (decreased wakefulness and increased focal lesions); the need for long-term CSF drainage using EVD.
due to the intolerance of its overlapping in children or increase in the level of installation in the form of sharp deterioration in neurological status; formation of large pseudomeningoceles with the risk of wound liquorhea not caused by a suture defect of the operating wound.

The need for the bypass surgery was evaluated within the first month after tumor resection (generally accepted terms of the early postoperative period), since the development of intracranial hypertension during later terms can be a consequence of adjuvant therapy (if it is a malignant tumor requiring specialized oncological treatment) or tumor recurrence.

For analysis and identification of factors increasing the risk of development and/or persistence of hydrocephalus symptoms in the postoperative period, all children were divided into several groups by age and histogenesis. The children were divided into four groups based on the histological nature of the tumor: group 1 consisted of children with piloid astrocytomas of the PCF; group 2 included children with medulloblastoma of the PCF; group 3 included patients with anaplastic ependymomas of the PCF; group 4 was represented by other space-occupying formations. Each group was further divided based on the age into a group of children older than 3 years and a group of children younger than 3 years. In addition, the effect of repeated surgical resection of the PCF tumor on the risk of persistent hydrocephalus and the subsequent need for VPB was assessed by comparing the obtained data with the data for primary operated children.

Results

Mean age of the patients was 6.4±4.2 years (6 months to 18 years). The group of children under the age of 3 included a total of 32 children, and 123 children were older than 3 years. There were 36 children who were repeatedly operated on for the PCF tumor. Indications for shunt placement in the postoperative period appeared in 13 (8.4%) patients.

Group 1 included 57 children with piloid astrocytomas of the PCF, their mean age was 6.9±4.1 years, 7 (12%) of which were younger than 3 years. Group 2 consisted of 55 children with medulloblastomas of the PCF, their mean age was 6.5±3.6 years, 8 (15%) of the children of this group were under 3 years of age. There were 23 children with anaplastic ependymomas of the PCF in group 3, their average age was 4.9±3.8 years, 10 (43%) of them were under age of 3. Group 4 had the most diverse pathology: dermoid cysts, atypical teratoid-rhabdoid tumors, primitive neuroectodermal tumors (PNET), ependymomas, hemangioblastomas, meningiomas, gangliogliomas, ganglioastrocytomias, choroid papillomas, glioblastomas. This group included 20 children with the average age of 6.4±5.8 years, 6 (30%) children were under the age of 3.

Having analyzed the data for all of the 4 groups, we obtained the following results. There were no cases requiring shunt surgery in the first group of children with piloid astrocytomas. Meanwhile, 9 (16%) cases required repeated intervention.

The need for shunt surgery appeared in 9 (9.1%) cases in the group 2. All 5 patients were older than 3 years and were primary patients. As in case of the first group, 9 (16%) children of the second group underwent repeated surgery.

In group 3, the need for VPB in the early postoperative period occurred in 5 (22%) cases. Of these 5 children, 2 were younger than 3 years, 4 had a repetitive surgery. In total, 19 (61%) children were reoperated on in this group.

In group 4, shunt placement was required in 3 (15%) cases. One case included a child under the age of 3 who had been operated on for dermoid cysts of the PCF, 2 of the remaining cases were children older than 3 years who had been operated on for ganglioastrocytoma and atypical teratoid-rhabdoid tumor of PCF.

The need for shunt placement in children with various histology is summarized in Fig. 1.

Statistical analysis of the data showed:

— no statistically significant difference in the development of postoperative hydrocephalus between patients with primary and repeated surgeries (χ2 criterion, \(p=0.174\)) (Fig. 2):

— no statistically significant difference between the age groups of children younger and older than 3 years (χ2 criterion, \(p=0.821\)) (Fig. 3).

Analysis of different histological groups showed:

— a weak negative correlation of the need for the VPB in piloid astrocytomas (Pearson correlation coefficient, \(p=0.011\));
— a weak positive correlation of the need for the VPB in anaplastic ependymoma (Pearson correlation coefficient, \( p=0.035 \)).

In order to determine the significance of factors, a logistic regression model was constructed. As expected, this model did not confirm a significant effect of any of the factors on the risk of persistent hydrocephalus, except for the histological diagnosis of “piloid astrocytoma”. The following odds ratios were obtained with 95% confidence intervals: OR 0.95 (95% CI 6.6—6.5) for the age group of over 3 years of age; OR 0.001 (95% CI 13.2—0.07) for the histology of “piloid astrocytoma”; OR 1.33 (95% CI 6.3—6.9) for repeated surgery.

**Discussion**

Our data confirm the existence of persistent hydrocephalus in the early postoperative period after PCF tumor resection despite removal of CSF occlusion. However, the necessity of a permanent CSF shunt placement after PCF tumor resection is much lower in our study (8.4%) than in the published literature (18—40%) [3—9]. We have not found a significant relationship between the patient’s age and the risk of persistent hydrocephalus. Similar results can be found in a series of foreign papers [4, 5, 17].

According to our data, the main factor that increases the risk for the necessity to perform shunt surgery after surgical resection of the tumor is the histological nature of this tumor. Children with anaplastic ependymomas of the PCF are included in the group with the highest risk of development and persistence of hydrocephalus symptoms and require VPB in 22% of cases. Children with medulloblastoma comprised the group with an average risk, and the proportion of patients requiring shunt placement was 9%. Patients with piloid astrocytomas did not require shunt surgery in our series. Hydrocephalus signs regressed after tumor resection in all children with piloid astrocytomas. In this regard, these children were included in the group with a minimal risk for requirement of VPB after tumor resection. These data are consistent with a number of foreign studies [5, 17].

Some researchers suggest using endoscopic third ventriculostomy (ETV) as a prophylactic measure prior to PCF tumor resection or during surgery in order to reduce the number of bypass patients [2, 9, 11—15]. If such tactics are extrapolated to our data (155 patients with PCF tumors and signs of occlusive hydrocephalus) and ETV is performed in all patients with signs of intracranial hypertension prior to tumor resection, more than 140 unnecessary surgeries would be performed, since only 13 (8.4%) patients required bypassing. In addition, we are convinced that impaired CSF resorption is the main pathogenesis of persistent hydrocephalus in our practice. It is very likely that the number of required VPB interventions would remain unchanged in such case. We believe that prophylactic ETV in children with PCF tumors prior to tumor resection is unjustified, and if we consider the cause of hydrocephalus to be non-occlusive, then it is probably ineffective. Such tactics puts children at an additional risk of unnecessary surgery and leads to excessive and unreasonable expenditure of health resources.

The low values we obtained for persistent hydrocephalus in the early postoperative period after the PCF

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**Fig. 1.** The need for VPB in the early postoperative period after PCF tumor resection depending on the tumor histology.
tumor resection in children (8.4%) are most likely to reflect an improvement in the overall results of surgery for CNS tumors, including an increase in the radicality of tumor resection performed in the last 20 years.

Conclusion

In our retrospective study, histological nature of the tumor was the only statistically significant factor increasing the risk requiring shunt surgery after PCF tumor resection in children. Factors such as the patient’s age (older or younger than 3 years), number of surgeries (primary or secondary) were statistically insignificant. ETV is inadvisable for all children with PCF tumors who have signs of intracranial hypertension. The main method of resolving hydrocephalus in children with PCF tumors is tumor resection. Dehydration and steroid therapy is the optimal choice in case if it is impossible to perform the surgery immediately after the diagnosis is made. External ventricular drainage with further decision on the transfer of the patient to a specialized hospital is required in case of severe occlusive hydrocephalus. Shunt surgery or ETV can be recommended as a first measure only in case of impossibility to perform tumor resection in a patient with a clinical picture of worsening occlusive hydrocephalus.

Authors declare no conflict of interest.

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The study is devoted to the important problem of pediatric neurosurgery: treatment of patients with tumors of the posterior cranial fossa and concomitant hydrocephalus. There is still no uniform approach to the treatment of these patients in Russian hospitals.

It has been convincingly demonstrated once again on a large clinical material that tumor resection is the main method of treating pediatric hydrocephalus. Edema regresses in more than 90% of patients, and no shunt placement is required. This proves that any CSF shunt or endoscopic third ventriculostomy justified? Endoscopic third ventriculostomy in children with posterior fossa tumors and hydrocephalus. There is still no uniform approach to the treatment of these patients in Russian hospitals.

The study demonstrated that the patients’ age and previous interventions do not correlate with the indication for shunt surgery. Some correlation has been shown between tumor histology and the risk of hydrocephalus progression. However, there has been no analysis of the importance of such factors as radicality of tumor resection, complications of the perioperative and postoperative periods (pneumocephalus, postoperative hematomas, liquorhea, meningitis), metastases in the brain or spinal cord. Is it possible to exclude that these factors affect preservation of hydrocephalus diagnosis in the greatest degree?

The work poses several important questions the surgeons face on a daily basis but does not answer them. The first question is what actions should be undertaken if a child with severe hydrocephalus is in a clinic where there is no way to perform tumor resection? If the terms and patient’s condition allow his transportation, the child should be transferred to the federal center. But what if the condition is severe, and the transfer to another clinic is delayed? Endoscopic third ventriculostomy would be an ideal solution. However, tumor resection can be performed in the clinics with the technology of endoscopic surgeries! In these cases, when the solution cannot be found, shunt surgery, is apparently, the lesser of evils. It will allow a surgeon to save some time, stabilize the child’s condition, to have the opportunity to transport him to another city. External ventricular drainage is the worst solution to the problem: transportation of the patients with external ventricular drainage often results in meningitis, liquorhea, spontaneous removal of drainage in an airplane or train.

The second question follows from the first one. What actions should be undertaken in case of the shunt system has been already installed after tumor resection? Removal of the system would be a good solution. However, no one knows how much the child becomes dependent on the shunt. In large federal clinics, this problem is being handled by doctors at the place of residence, who, as a rule, leave the situation unchanged.

There are other interesting aspects of this topic. For example, there are the features of conducting intraventricular chemotherapy in the presence of the installed ventriculoperitoneal shunt. Thus, the presented work has multiple aspects, it is very relevant and provides important information for further research works.

S.S. Ozerov (Moscow, Russia)
Li-Fraumeni Syndrome in a Patient with Multiple Anaplastic Oligodendrogliomas of the Brain (Case Report and Literature Review)

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Li-Fraumeni syndrome (LFS) is a clinically and genetically heterogeneous hereditary syndrome with predominantly oncological manifestations, which is associated with mutations in the TP53, MDM2, and CHEK2 genes. The most common variant is a TP53 mutation.

Objective — to analyze the literature and present a clinical case of a patient with Li-Fraumeni syndrome and multiple anaplastic oligodendrogliomas of the brain.

Clinical case. A 42-year-old male patient presented with complaints of headaches, word finding difficulty, memory loss, right hemianopsia, and generalized convulsive attacks. For 10 years, he underwent multiple interventions and chemotherapy courses for colon adenocarcinoma and recurrent B-cell lymphoma. MRI revealed multiple space-occupying lesions of the cerebral hemispheres, which were located in the left temporo-occipital and right frontal regions.

Results. The patient underwent resection of multiple space-occupying lesions of the left temporo-occipital and right frontal regions. The postoperative period proceeded without complications. The histological diagnosis was WHO grade III anaplastic oligodendroglioma. The patient and one of his sons were detected with a R248W missense mutation in the TP53 gene. The patient underwent six courses of temozolomide chemotherapy. At a follow-up examination 20 months after surgery and chemotherapy, the patient’s condition was satisfactory; he returned to work. Control MRI of the brain revealed no signs of continued tumor growth.

Conclusion. An analysis of the literature and the clinical case indicate the success of multiple surgical interventions and chemotherapy courses performed for a long time in the patient with Li-Fraumeni syndrome manifested by colon adenocarcinoma, recurrent B-cell lymphoma, and multiple anaplastic oligodendroglioma of the brain. The patient had a good quality of life and returned to professional activity.

Keywords: Li-Fraumeni syndrome, TP53, multiple primary malignant cerebral neoplasms.

Abbreviations:
LFS — Li-Fraumeni syndrome
5-ALK — 5-aminolevulinic acid
MRI — magnetic resonance imaging

Li-Fraumeni syndrome (LFS) is a clinically and genetically heterogeneous hereditary syndrome with predominantly oncological manifestations, which is associated with mutations in the TP53, MDM2, and CHEK2 genes. The most common variant is a TP53 mutation. This gene has very important protective function as it realizes its anti-oncogenic role through regulation of a number of cellular processes. Moreover, even though it does not have tissue specificity, it is a key regulator of the cell cycle in most tissues. It explains the wide spectrum of malignant neoplasms emerging in LFS, the most common of which are soft tissue sarcoma, leukemia, breast cancer and brain tumors [1, 2].

Neoplasms of the brain are found in 11% of LFS patients; in women they are detected only in 6% of cases, while in men they are detected in 19%. A total of 49% of patients with one tumor pathology develop at least one more oncological disease within 10 years. Neoplasm of the brain accounts for 8% of the secondary tumor processes. The highest risk for their occurrence in LFS is observed in men older than 45 years [3].

The objective of the present study is to analyze the literature and describe a clinical case of a patient with Li-Fraumeni syndrome and its rare manifestation, multiple anaplastic oligodendrogliomas of the brain.

Clinical case. A 42-year-old patient was hospitalized to Burdenko Neurosurgical Institute on June 14, 2016. He was admitted with complaints of headache, difficulties with word selection, memory loss, and deterioration of the right half of the field of vision that occurred in early May 2016. At the end of May, he had a generalized seizure. The seizures were subsequently repeated 2-3 times a day. He did not receive any anticonvulsant therapy. MRI of the brain revealed multiple space-occupying lesions in the left temporo-occipital and right frontal regions.
At the time of hospitalization, the patient was conscious, communicative, with reduced criticism regarding his condition. There was a pronounced cephalagic syndrome, signs of intracranial hypertension (stagnant discs of optic nerves with hemorrhages on the fundus), right-sided homonymous hemianopsia (with a large prolapse of the nasal half of the left eye field of vision). In addition, the patient displayed signs of acoustic-mnemonic aphasia, dyslexia, dyscalculia, impaired attention and visual-spatial gnosis.

When collecting medical history, it was found out that in 2007 the patient underwent a removal of adenocarcinoma of the rectum with the formation of colostomy. An increase in the lymph nodes of the supraclavicular area was detected after 3 courses of capecitabine monotherapy. Biopsy revealed B-cell lymphoma from small lymphocytes (CD20+). Lymphadenectomy was performed followed by 7 courses of polychemotherapy (fluorurabine + cyclophosphamide). Clinico-radiological remission was achieved. In 2008, the colostomy was closed. Dynamic observation revealed a relapse of B-cell lymphoma in May 2012. Five courses of polychemotherapy (rituximab + fluorurabine + cyclophosphamide) were performed followed by rituximab monotherapy until August 2014 with a good clinical effect.

A molecular genetic study conducted in the "Medical Genetic Science Center", revealed a R248W missense mutation in the TP53 gene. The presence of LFS with a similar mutation in the TR53 gene was also discovered in one of the patient’s sons, who underwent combined treatment for osteosarcoma of the lower wall of the right orbit, paravertebral rhabdomyosarcoma and liver angioma (Figure 1).

MRI of the brain (16.06.16) in T1, T2, T2-FLAIR, DWI, and ASL-perfusion modes revealed diffusely growing intracerebral structures that heterogeneously and intensively accumulate contrast in the left tempo-occipital and right frontal regions. The pathological focus in the left hemisphere caused the displacement of the median structures to the right by 13 mm and compressed the left leg of the brain. MRI-spectroscopy revealed a sharp increase in the choline peak (Cho), a decrease in the peak of N-acetylaspartate (NAA), and the appearance of the lipid/lactate peak (Lip/Lac) in the zone of contrast enhancement in the tempo-occipital region to the left.

According to the conclusion of a neuroscientist, multiple space-occupying lesions of the brain structures most similarly correspond to Grade III—IV gliomas (Figure 2).

Taking into account the multiple nature of brain lesions with signs of a rough lateral dislocation, intracranial hypertension, the history of tumors of a different histological nature (adenocarcinoma, recurrent B-cell lymphoma) it was decided to conduct surgical treatment in several stages.

First, the largest tumor in the occipital lobe on the left was removed using fluorescent diagnostics and intraoperative neurophysiological monitoring (Fig. 3). The patient’s response to the surgery was satisfactory and the wound healed by primary healing.

Histological and molecular genetic studies

Morphological examination revealed a glial tumor which consisted of cells with an optically empty cytoplasm, polymorphic nuclei, with the presence of dense cell sites where few mitotic figures were observed, which is vascularized with thin vessels; the initial manifestations of endothelial proliferation were visualized in few vessels (Fig. 4a). Immunohistochemical study revealed a positive expression of the gliofibrillar acid protein GFAP, total expression of MAP-2 (see Figure 4b), positive expression of p53 in 30—40% of the nuclei of tumor cells (see Figure 4c). There was no expression of the total leukocyte antigen CD45 and IDH1 R132H, which indicates the absence of the mutation of the IDH1 R132H gene. The labeling index of the proliferative marker Ki-67 ranged from 8 to 10% (see Figure 4d). The molecular-genetic study using fluorescent in situ hybridization revealed a balanced profile of chromosomes 1, 4q, 7 and 19 with the tendency of all chromosomes towards small polysomy. There were no signs of cooperative deletion of 1p19q and amplification of EGFR and PDGFR genes. Thus, the morphological picture and immunophenotype corresponded to anaplastic oligodendrogloma (WHO Grade III) wt IDH1 without the cooperative deletion of 1p19q.

Subsequently, the tumor was removed from the medial parts of the left temporal and right frontal regions using neurophysiological monitoring and ultrasound navigation. Pathohistological study showed that the tumor tissue is identical to the biopsy from the previous surgery.

Immunohistochemical study revealed negative expression of IDH-1R132H, positive expression of MAP-2, IM Ki-67 up to 8%, positive expression of p53 in 30—40% of nuclei. Conclusion: WHO grade III anaplastic oligodendrogloma.

On the 7th day after the last surgery, the patient was discharged in a satisfactory condition. No negative dynamics were observed in the neurological status. Given the multiplicity and extent of brain damage, as well as the persistence of signs of intracranial hypertension in the form of moderately expressed congestive optic discs on the fundus, a radiologist advised against radiation therapy. A chemotherapist prescribed a monotherapy with temozolomide 400 mg (5/23), in a total of 6 courses.

Within the next 1 year and 8 months after the neurosurgical interventions and 10 years after the first manifestation of the disease, there was no evidence of tumor recurrence. Already in September 2016 (2 months after the discharge) the patient returned to work and he now con-
continues to work in his field (engineer) in a managerial position.

According to the results of the neuropsychological examination, there is a positive trend in the form of regression of the aphasic disorder with the preservation of some elements of amnestic aphasia, dyscalculia, and a light decrease in cognitive functions. Dynamic neurological examination revealed complete regression of congestive optic discs, however the lesion of the visual pathway in the left hemisphere of the brain persists (full right-sided homonymous hemianopsia). The control MRI revealed no signs of continued growth of intracerebral tumors (Fig. 5).

Discussion

LFS had first been described more than 40 years ago as a family tumor syndrome, which is characterized by development of pediatric rhabdomyosarcoma [4]. Familial predisposition to oncological processes in LFS is associated with early onset of breast cancer, soft tissue sarcoma, adrenocortical tumors and brain tumors. Over the time, the concept of LFS has been expanded to include greater number of clinical manifestations, and the concept of the etiology of the syndrome was also expanded [5].

Epidemiological studies show that in families with LFS, the risk of developing tumors throughout the life-time is 73% for men and 100% for women [6]. The diagnosis of this disease includes identification of the congenital mutations in the TP53 gene by genetic testing in families with suspected LFS. Congenital mutations associated with LFS are similar to the somatic mutations observed in sporadic tumor cells and affecting the p53 protein gene (TP53). TP53 is a suppressor gene of cell proliferation, and mutations of TP53 gene are most often inherited by an autosomal dominant pathway [7].

In addition, families with clinical manifestations and an inheritance pattern typical of LFS were discovered who did not have mutations in the TP53 gene, which demonstrated the role of other genes such as MDM2 and CHEK2 in the development of this pathology. This served as the basis for distinguishing three types of LFS [8]. In the clinical case described above, the patient has type 1 LFS arising from the dominant missense mutation in the TP53 gene (R248W missense mutation).

There could be different mutations of this gene, which are important for the development of oligodendrogliomas. One of the most frequent is the single nucleotide replacement rs78378222 located in the 3’-untranslated region of TP5362 which is associated with high risk of oligodendroglioma [9, 10]. This relatively rare allele (about 1% in the European population) gives a threefold increase in the risk of glioma. Moreover, the variant of mutational changes observed in this patient rarely becomes the cause of anaplastic oligodendroglioma, which makes the presented clinical observation quite remarkable.

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Cancers in parents carrying mutations in TP53 gene:
- adenocarcinoma of the rectum,
- B-cell lymphoma in the right shoulder area
- multiple brain neoplasms

Parents

Patient
carrier of mutation in TP53 gene

Wife
Healthy

Children
carrier of mutation in TP53 gene

Cancer in a child carrying mutation in TP53 gene:
- osteosarcoma of the lower wall of the right orbit
- PNET / rhabdomyosarcoma paraverebral, Th10-11 level
- liver angioama

Healthy

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Fig. 1. Family history of a patient with Li-Fraumeni syndrome.
Fig. 2. MRI examination of the brain in a patient with Li-Fraumeni syndrome before the surgery.

MRI in the axial projection in the T2 (a, b), T2-FLAIR (c, d) and T1 (d, e) modes reveals the intra-cerebral diffusely growing space-occupying lesions of the heterogeneous structure in the left temporo-occipital region and the right frontal lobe. The mass lesion in the left occipital lobe has more intense MRI-signal in diffusion mode (f). The volumetric blood flow in tumors of the left occipital and right frontal lobes was increased with ASL-perfusion up to 88 and 70 mL/100 g/min, respectively (g, h). The space-occupying lesions heterogeneously and intensively accumulate a contrast agent (i-l).
**Fig. 3. Intraoperative photos at the stages of the surgical intervention.**
a, b — the initial stage of the tumor removal: a — in white light, b — in fluorescence mode (BL 400), intense glow of tumor tissue; c, d — after the tumor removal: c — in white light, d — in fluorescence mode (BL 400), there is no apparent glow in the area of the removed tumor.

**Fig. 4. Histological specimen of the tumor.**
a — staining with hematoxylin and eosin, ×200 magnification. Tumor tissue consisting of polymorphic cells with rounded, focal hyperchromic nuclei and optically empty cytoplasm; the initial phenomena of endothelial proliferation in the vessels; b — immunohistochemical study, ×200 magnification. The labeling index of the proliferative marker Ki-67 is 8-10%; c — immunohistochemical study, ×200 magnification. Expression of p53 is observed in 30—40% of the nuclei of tumor cells; d — immunohistochemical study, ×200 magnification. Positive total expression of MAP-2 by tumor cells.
The problem of managing patients with LFS is currently highly relevant. Modern tactics consist of early diagnosis of neoplasms and, if possible, complete surgical resection of tumors with subsequent adjuvant therapy [11].

In case of oligodendrogliomas with mass effect, regardless of the degree of malignancy, radical tumor removal with maximum preservation of functionally significant structures reduces the severity of symptoms and prolongs life expectancy [12, 13].

Fig. 5. MRI examination of the brain of the patient with Li-Fraumeni syndrome after 1 year and 8 months after neurosurgical interventions. MRI in the axial projection in T2 (a, b), T2-FLAIR (c, d), T1 (d, e) modes, and also in T1 mode after the introduction of the contrast (g-i) reveal postoperative cerebrospinal cavities in the left temporo-occipital region and right frontal lobe without signs of pathological accumulation of the contrast medium. There were no MRI data in support of the continued growth of tumors.
In this clinical observation of a patient with multiple anaplastic oligodendrogliomas of the brain, the first stage of treatment consisted of the maximal resection of tumor nodes using metabolic fluorescence diagnostics with 5-aminolevulinic acid (5-ALA). Fluorescent diagnostics with 5-ALA helps surgeons to identify the true boundaries of gliomas, which contributes to the most complete removal of pathological tissue [14—18]. In case of the resection of the contrast-accumulating part of Grade III—IV gliomas (according to postoperative MRI with contrast enhancement) and the absence of residual fluorescence at the end of the main stage of the surgery, the overall survival of patients is higher than in the similar situation, but with the presence of residual fluorescence [19].

Patients with oligodendroglial Grade III tumors, who have been diagnosed with 1p19q cooperative deletion, have the most favorable prognosis. If there is a deletion of CDKN2A, PTEN genes, amplification of EGFR gene or their combinations in the tumor, the prognosis is less favorable. Simultaneous or sequential use of radiotherapy and chemotherapy after surgical treatment in patients with oligodendroglial Grade III tumors allows to achieve the best survival rate [20—22]. In the described clinical case, radiation treatment was not performed due to large amount of brain damage.

Immunohistochemical study of the patient’s biopsies revealed negative expression of IDH 1R132H, positive expression of MAP-2, 1M Ki-67 up to 8%, positive expression of p53 in 30—40% of nuclei. There were no signs of cooperative deletion of 1p19q and amplification of EGFR and PDGFA genes.

Among the chemotherapeutic approaches, the greatest experience is accumulated in the use of PCV scheme (procarbazine 60 mg/m² IV, lomustine 110 mg/m² orally, vincristine 1.4 mg/m² IV) as a 29-day cycle, which is repeated every 6 weeks [14, 23, 24]. The high efficacy of temozolomide has been demonstrated for recurring anaplastic oligoastrocytomas [25]. In this case, 6 courses of temozolomide monochemotherapy (recommended dose of 200 mg/m², actual dose 400 mg (4 capsules of 100 mg) daily (po) for 5 days followed by a break of 23 days) were used.

An analog of our observation can be found in a paper by M. Guidi et al. [26], in which the authors describe an LFS patient with cerebral gliocarcinoma. The removal of the tumor of the right parietal lobe was followed by radiation therapy (59.4 Gy/1.8 Gy) and chemotherapy with temozolamide. After 24 months, the patient’s condition was satisfactory, with no signs of a relapse of the disease.

Such cases demonstrate the importance of early and accurate diagnosis of hereditary tumor syndromes, such as LFS, as well as the need to develop effective preventive and curative approaches. Genetic diagnosis of the embryo during extracorporeal fertilization can be used as a primary LFS prevention [27—29]. There have been publications on gene therapy approaches in treatment of patients with TP53-associated tumors in LFS with genetically engineered constructs in a form of a replication adeno-virus vector bearing the wild-type TP53 gene and the cytomegalovirus promoter [30].

What can we do now for a patient with diagnosed mutations in the TP53 gene using our traditional methods of diagnosis and treatment? First, assess the risk of development of malignant neoplasms based on clinical history (taking into account the specificity of malignant neoplasms in the family), neurological status, laboratory and instrumental diagnostic methods, the scope of which depends on the family history of tumors; secondly, conduct medical and genetic consultations of relatives of 1st and 2nd degree of kinship, and, if necessary, of all members of the family. Recommendations for the genetic testing and observation of patients with mutations in the TR53 gene have been developed by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) [11]. According to them, adults and children diagnosed with mutations in the TP53 gene should pay attention to appearance of pain symptoms, be under the dynamic supervision of oncologists who are aware of the high risk of development of rare, including primary, malignant tumors; adult women should be seen by a mammologist from the age of 18 with mammography and MRI of the mammary glands from the age of 20—25 or 5—10 years before the age of detection of breast cancer in a relative of the 1st and 2nd degree of kinship; adults, starting from the age of 25, should undergo screening of the gastrointestinal tract (ultrasound and computed tomography of the abdominal organs), blood tests for tumor markers and endoscopic examinations every 2 years.

Conclusion

The Li-Fraumeni syndrome is a rare hereditary disease with mainly oncological manifestations associated with mutations in the TP53 gene (the most frequent variant), MDM2 and CHEK2. The need for a multidisciplinary medical approach to diagnosis, treatment and prevention in patients with this syndrome is justified by its clinical and genetic heterogeneity.

Despite the severity of the genetic defect and the malignant nature of most tumors, thorough medical examination and timely comprehensive treatment of emerging tumors using modern intraoperative monitoring technologies, performing the most radical surgical interventions, radiotherapy and chemotherapy provide an increase in the duration and improvement of the quality of life of patients.

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Authors declare no conflict of interest.
The work of the team of authors is devoted to the description of a rare clinical observation of a patient with Li-Fraumeni syndrome and multiple space-occupying lesions of the brain. Li-Fraumeni syndrome (LFS) is a clinically and genetically heterogeneous hereditary syndrome with predominantly oncological manifestations, which is associated with mutations in the TP53, MDM2, and CHEK2 genes. The most common variant is a TP53 mutation.

The paper provides a detailed description of a 42-year-old patient who, together with one of his two sons, had a missense R248W mutation in the TP53 gene, and had previously been treated for adenocarcinoma of the large intestine and recurrent B-cell lymphoma. In 9 years after the first performed surgery on the intestine, magnetic resonance imaging of the brain revealed multiple space-occupying lesions in the left temporo-occipital and right frontal regions and they were successfully removed (histology: WHO Grade III anaplastic oligodendroglioma). The patient was followed up for 1 year and 8 months; control MRI of the brain with contrast enhancement revealed no signs of continued growth.

The authors provide a review of the literature describing Li-Fraumeni syndrome and the necessary methods of genetic counseling for patients.

This work is an example of successful treatment of a patient with multifocal brain damage against a background of a rare genetic disease and will be useful to practical neurosurgeons and neurologists.

V.L. Puchkov (Moscow, Russia)
According to the classification system proposed by E. Fisher, anterior cerebral artery (ACA) aneurysms are named with respect to artery segments and are subdivided into proximal ACA aneurysms (the A1 segment), ACA–AcomA aneurysms, aneurysms of the proximal region of the pericallosal artery (the A2 segment), the "classical" pericallosal aneurysms (the A3 segment) being formed within the genu of corpus callosum, and distal ACA aneurysms (the A4 and A5 segments) [1, 2].

A2 segment aneurysms are extremely rare. According to the literature data [3, 4], they account for 0.2—1.0% of all intracranial aneurysms. Distal aneurysms in the ACA territory usually arise in the embouchement of frontopolar or medial frontal arteries and have a saccular-shape appearance. There are only sporadic reports on fusiform-shaped aneurysms. In this study, we present a case report of a female patient with a large fusiform aneurysm of the A2 segment of the left ACA, who had undergone proximal (Hunter's) aneurysm clipping with an intraoperative awakening.

Case report

A 23-year-old female patient B. was recommended by an endocrinologist to undergo cerebral MRI as she had an irregular menstrual cycle. Examination by MRI and helical CT angiography revealed a large (16 mm) bean-shaped aneurysm in the A2 segment of the left ACA (Fig. 1).

The long-standing experience has demonstrated that surgical clipping of fusiform aneurysms is not justified, since a de novo aneurysm is often formed after the surgery within the arterial wall that has not been isolated from the circulation. In this case, deconstructive surgeries are a radical solution; if needed, they are also combined with creation of vascular anastomosis. Endovascular arterial reconstruction using a flow-diverting stent or endovascular balloon occlusion of the artery are other effective surgical techniques.

In the reported case, the plan of surgical intervention involved two stages: (1) performing the pterional access and test temporal isolation of the left ACA A2 segment from circulation with intraoperative awakening of the patient to assess the motor and language functions; (2) if neurological symptoms have emerged, performing the frontal interhemispheric approach and creating an A3—A3 side-to-side interarterial anastomosis between the right and left ACAs (Fig. 2).

Skin incision and the access were performed from the right side, which allowed us to carry out a contralateral approach to the A2 segments and to ensure right-side access window to the genu of corpus callosum. The surgery was discussed in detail with the patient. The awakening and test clipping stages were assessed together with an anesthetist the day before.

Surgical intervention. The patient received no premedication before being taken to the operating room. Anesthesia was induced by bolus injection of propofol (2.5 mg/kg) and fentanyl (1.5 µg/kg). A laryngeal mask

Abbreviations:
CT — computed tomography
MRI — magnetic resonance imaging
ACA — anterior cerebral artery
AcomA — anterior communicating artery
airway was placed and mechanical ventilation was started. Analgesia involved scalp block with 10 mg/mL ropivacaine (20 mL) and infiltration of the incision line and the sites where neurosurgical head holder pins were inserted. Depth of anesthesia was controlled by BIS monitoring.

The conventional right-sided pterional craniotomy was performed through a semi-circle skin incision in the frontotemporal brain region. Prior to making the incision, the dura mater was also anesthetized with ropivacaine. An approach to the right cranial nerve II was performed; the chiasmatic and carotid cisterns were opened. The ICA was isolated up to the bifurcation point and the A1—A2 angle was accessed. Right-sided subpial resection of the gyrus rectus was performed; the A1 and A2 segments were exposed from both sides. The left A2 segment at the aneurysmal neck was isolated from the circulation with a temporary clip. Patient’s awakening from anesthesia was started. Ten minutes later, the patient became contactable; she was able to clasp both hands and move her feet upon request. The patient was able to produce clear speech 17 minutes later: upon request, she counted from 1 to 10 and answered the questions about her relatives’ names, place of employment, etc. Overall, test proximal clipping lasted 22 minutes; no focal neurologic deficit was detected during the surveillance period. The left ACA A2 segment was isolated from circulation with a permanent clip. The anesthesia was deepened; hemostasis was achieved; and the wound was closed layer-by-layer.

The postoperative period was uncomplicated; no neurological deficit was observed. On day 1, a cranial CT scan showed thrombosis of the aneurysm. Selective carotid angiogram demonstrated no contrast filling of the left ACA starting from the A2 segment (Fig. 3). The patient was discharged to be followed up by a neurologist in the local health facility.

A follow-up examination performed 2 months after surgery showed that the patient was in satisfactory condition. She did not experience any limitations in her daily activities and returned to work.

Discussion

ACA is one of the two terminal branches of the internal carotid artery (ICA), which is subdivided into the precommunicant and postcommunicant segments. The proximal precommunicant segment, lying between the bifurcation point of the ICA and the embouchement of the AcomA is denoted as the A1 segment. The distal part
is divided into the A2 (infracallosal), A3 (precallosal), A4 (supracallosal), and A5 (postcallosal) segments.

The A2 ACA segment is known to consist of three major branches: the recurrent artery of Heubner, the medial frontobasal, and frontopolar arteries. They are differentiated in angiograms mostly according to the areas supplied with blood, since these arteries significantly vary in terms of their diameter and the site of origin. The entire A2 segment lies below the free edge of the falx cerebri, which allows one to move the vessels freely beyond the midline and access both A2 segments through the unilateral approach.

The anatomy of the ACA may significantly vary. The most common developmental abnormalities of the anterior part of the circle of Willis are hypoplasia and aplasia of the ACA (one of ACA being either thinned or absent), fenestration of AcomA, azygos ACA, unilateral ACA (the A1 segment gives off both pericallosal arteries, while the other ACA is usually hypoplastic), duplicated ACA (three pericallosal arteries caused by unilateral duplication of the A2 segment), etc. In our practice, we use the classification proposed by E. Fisher, which takes into account the aneurysm location with respect to the genu of corpus callosum and stable ACA branches (the callosomarginal and pericallosal arteries). All ACA aneurysms located distal to the AcomA are classified as peripheral (distal) aneurysms. Surgical anatomy of distal aneurysms was previously described in detail in publications by M. Putsilllo, I. Sazonov, M. Lehecka, and R. Dashti [1—8].

Peripheral ACA aneurysms are small, wide-necked, and are typically formed in the embouchement of ACA branches. They are often combined with aneurysms of other localization, arteriovenous malformations and other abnormalities of development of cerebral vessels.Peripheral ACA aneurysms, and the pericallosal ones in particular, are not rare: they are found in 2—9% of cases. Nevertheless, there are very few case reports of treatment of fusiform aneurysms involving the A2 segment. In the largest-scale study by M. Lehecka et al. [8] focused on peripheral ACA aneurysms, only 3 (1%) of patients had fusiform aneurysms.

Fusiform aneurysms are spindle-shaped diffuse dilatations of arteries, which usually occur in the vertebrobasilar arterial region or ICA territory. Fusiform aneurysms typically present with symptoms characteristic of pseudotumor cerebri or clinical signs of thromboembolism. It still has to be elucidated why these aneurysms are formed. A. Day et al. [9] mentioned that cerebral atherosclerosis and arterial wall dissection are the factors con-

Fig. 3. Patient B. CT of the cerebral vessels on postoperative day 1.

a — hyperdense signal from the aneurysm indicates that it was thrombosed; b — lateral view of the control left-side carotid angiogram: the angiogram shows no contrast filling of the left pericallosal artery.
ttributing to formation of these aneurysms. Systemic connective tissue disorders, such as von Recklinghausen’s disease, fibromuscular dysplasia, etc., also play a role in pathogenesis of aneurysms. Most neurosurgeons prefer to treat fusiform aneurysms operatively. As we have mentioned previously, the conventional clipping is ineffective, since the unprotected aneurysm wall is dilated over time and may result in hemorrhage.

The literature data [10, 11] indicate that deconstructive surgeries are associated with a high risk of de novo aneurysm formation (0.3—3.3%). Follow-up of unruptured aneurysms showed that their growth is an individual problem: S. Ferns et al. [12] reported that MR angiography revealed aneurysm growth in 7.9% of patients over a 5-year-long follow-up period. The question what contributes most — whether it is worsened hemodynamic stress, genetic weakness in the vessel wall, or some other reasons — is yet to be answered. Today, the only 100% confirmed fact is that smoking, hypertension, connective tissue disorders, and infections contribute to a certain extent to de novo aneurysm formation [10—14].

Moreover, new aneurysms can be formed several years after the surgery both in the same and in a different vascular territory, both after clipping and after creation of an anastomosis. Thus, O. Arnaout et al. [15] reported a case of formation of a large fusiform aneurysm in the basilar artery 7 years after ICA deconstruction to manage a giant cavernous ICA aneurysm. In their turn, T. Kurokawa et al. [16] presented two case reports of aneurysm formation in the MCA within the area of extra—intracranial microanastomosis created in combination with ICA occlusion.

Many neurosurgeons successfully use neurophysiological monitoring when performing surgeries associated with a high risk of developing motor deficit. Nevertheless, sensitivity, reliability, and consistency of the data obtained by monitoring the motor- and somatosensory-evoked potentials when performing surgical treatment of aneurysms are questioned. S. Abdulrauf et al. [17] revealed discrepancy between the neuromonitoring data and neurological symptoms observed upon awake surger-

REFERENCES


Conclusions

Proximal (Hunter’s) clipping of peripheral aneurysms is an efficient surgery that can be performed if collateral blood flow is sufficient. Both non-invasive preoperative methods (CT perfusion) and perioperative procedures (angiography with test artery occlusion, neuro-monitoring of motor-evoked potentials and somatosensory evoked potentials), as well as awake craniotomy, especially when assessing the language function, can be used to study the collateral blood flow and functional preservation of the brain depending on aneurysm features.

Authors declare no conflict of interest.
In neurosurgery, the established term "awake craniotomy" implies surgeries that involve patient's recovery from anesthesia to control the preservation of certain functions (language, motor or visual functions, etc.). Intraoperative electrophysiological monitoring is also typically employed, making it possible to achieve a significant extent of eradication of tumors residing in functionally important brain regions. The concept of awake craniotomy was first suggested in 1959 by J. De Castro and P. Mundeleer to refer to the method to improve the outcome of treating drug-resistant epilepsy. In 1994, M. Berger was among the first neurosurgeons to describe application of the awake craniotomy procedure in surgery of cerebral gliomas residing near the cortical regions involved in language and motor functions.

Awake craniotomy is currently used during resection of glial tumors adjacent to the cerebral cortex linked to speech (Broca’s and Wernicke’s areas). The key advantage of this technique is that it allows one to perform intraoperative brain mapping and obtain individual data on location of language centers, which allows one to achieve higher degree of tumor eradication and avoid neurological deficit.

The authors of this publication presented a case report of a female patient with a large fusiform aneurysm of the anterior cerebral artery (the A2 ACA segment). Surgical intervention involved occlusion of the ACA, which was intended to be combined with creation of A3—A3 interarterial anastomosis if collateral blood flow was insufficient. In order to evaluate the neurological functions, the authors used the procedure of patient awakening, while the ACA was temporarily clipped. This made it possible to make sure that the language and motor functions were preserved after the A2 segment had been clipped. The surgery was uncomplicated; no sequelae of ACA deconstruction were observed.

The reported clinical case is of an undoubted interest for vascular neurosurgeons. There are sporadic reports on using awake craniotomy to manage intracranial aneurysms. Most neurosurgeons use the conventional electrophysiological control methods or study the collateral blood flow using an ultrasonic flow meter or Doppler ultrasound methods.

Although the awakening procedure has a number of advantages, it should be emphasized that it induces a stressful situation for a patient, while its outcome is largely dependent on anesthetist’s skills and expertise. Awake surgeries are not devoid of complications, such as insufficient wakefulness, motor restlessness in the patient, nausea and vomiting, painful wound, epileptic seizures, etc. (A. Kulikov, 2015). It is clear that these interventions should be performed only if there are strict indications and other methods for assessment of neurological functions have proved inefficient.
Ischemic stroke (IS) is an important medical and social problem. The relatively high mortality rate, high level of disability, and the need to receive long-term hospital and post-hospital care make treatment of these patients rather resource-intensive, both for the healthcare system and for the state in general. Meanwhile, it has currently become possible to increase the number of favorable outcomes of the disease, as well as the percentage of patients not requiring help from other persons. Although having such limitations as the narrow therapeutic window, the relatively low percentage of successful outcomes of revascularization, and an impressive list of contraindications, revascularization of cerebral arteries during the acute phase of ischemic stroke using systemic thrombolysis has proved efficient. Mechanical thrombectomy using stent retrievers has become the next stage in recovery of blood circulation in the affected cerebral artery. This method has broadened the therapeutic window for revascularization and increased the percentage of favorable outcomes of this procedure. The refined diagnosis and neuroimaging algorithms have made patient selection more accurate, thus increasing the percentage of favorable outcomes. Mechanical thromboaspiration has also proved to be effective and safe when used both in combination with stent retrievers and independently.

**Evolutionary trends of thrombolytic therapy in patients with ischemic stroke**

In 1983, H. Zeumer et al. [1] reported successful revascularization of the basilar artery occlusion by intra-arterial (endovascular) infusion of streptokinase. In the 1980s, a series of experimental studies to identify the optimal thrombolytic drugs that can be used in acute cerebral ischemia and to determine their dosage was carried out [2, 3]. As a result, recombinant tissue plasminogen activator (rtPA) at doses ranging from 1.1 mg/kg in the ECASS (The European Cooperative Acute Stroke Study) to 0.9 mg/kg in NINDS (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study) started to be used in clinical studies as early as in the 1990s. When used at lower doses, the thrombolytic agent showed the same effectiveness. The results of the randomized multicenter trial ECASS were published in 1995. A total of 511 patients were randomized to groups receiving rtPA and placebo. The outcomes of the disease in the group treated with the thrombolytic agent were significantly better than in the placebo group, although there was no statistically significant intergroup difference in the 30-day death rates [4].

The NINDS trial [5], with its results also published in 1995, demonstrated that the chances for favorable outcome 3 months after ischemic stroke onset, were 50% higher in the group receiving systemic thrombolysis using 0.9 mg/kg rtPA than in the control group receiving placebo. A total of 624 patients were randomized to the groups treated with 0.9 mg/kg rtPA and placebo. The 3-hour therapeutic window between symptom manifestation and treatment initiation was found to be the time window when it was safe to perform systemic thrombolysis using this protocol. An attempt to broaden the therapeutic window to 6 h was made in the ECASS II study (the results were published in 1998). However, the level of hemorrhagic complications in this case turned out to be significantly higher and the 3-hour time window for systemic thrombolysis was not reconsidered after this study [6].

Nevertheless, the ECASS III trial (The Third European Cooperative Acute Stroke Study) [7] conducted 10 years later demonstrated that systemic thrombolysis can be performed safely and effectively during 4.5 hours since symptom manifestation. As a result, the therapeutic window in European and American clinical guidelines was broadened to 4.5 h.

In 2012, the Third International Stroke Trial (IST-III) involving 3035 patients (with 1617 patients being older than 80) showed no significant difference in treat-
ment outcomes in different age cohorts, including 80-year-old patients [8]. Taking into account the study by F. Mateen et al. [9] published in 2009, which demonstrated that thrombolytic therapy is unjustified in patients older than 90 years, we would like to summarize that systemic thrombolytic therapy using rtPA (0.9 mg/kg) is effective during the first 4.5 hours after manifestation of symptoms of acute ischemic stroke in patients younger than 90 years, unless there are known contraindications.

First-generation mechanical thrombectomy devices for treating patients with acute cerebral ischemia

Although the first report of successful revascularization of cerebral vessels in patients with acute cerebral ischemia described the endovascular procedure with a thrombolytic agent being intra-arterially infused into the verteobasilar arterial territory through a catheter, the endovascular method has not been routinely used to treat acute ischemic stroke for a long time. It was not until the mid-2010s that it started to be employed again. As technological progress had been made and endovascular tools have become more perfect, it was attempted to mechanically remove a thrombus from the cerebral arteries in patients with acute cerebral ischemia. However, the first-generation thrombectomy devices in patients with ischemic stroke yielded no positive outcomes for an appreciably long time. A breakthrough method that would be similar to implementation of systemic thrombolysis and would be superior in terms of effectiveness was not found. Furthermore, the results of three randomized trials to compare mechanical thrombectomy and systemic thrombolysis in acute ischemic stroke [IMS-III]10, SYNTHESIS (Local versus Systemic Thrombolysis for Acute Ischemic Stroke) [11], and MR RESQUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy)] were published by 2013 [12]. First-generation thrombectomy devices were mostly employed in each of these studies; however, none of the studies showed mechanical thrombectomy to be more effective than systemic thrombolysis.

Endovascular treatment of ischemic stroke: new era of stent retrievers

The situation has drastically changed after second-generation devices for mechanical extraction of thrombi from the cerebral arteries were developed. On March 3, 2008, Dr. Hans Henkes (Stuttgart, Germany) performed the first endovascular cerebral thrombectomy using a self-expandable intracranial stent electrotyically detachable from the delivery system. The Solitaire device (Medtronic, USA) was originally developed for stent assistance to manage the occlusion of wide-necked aneurysms with microcoils. Before the stent is detached from the delivery system, it can be repositioned or even removed from the vascular bed. Another design feature of the device is that the wall can be duplicated if the stent is inserted into a vessel being narrower than the nominal stent diameter. Furthermore, the device for treating complex intracranial aneurysms was rather delicately designed, making the risk of vessel wall injury very low. These features make it possible to capture the thrombus and to extract it from the artery, leaving a low risk of arterial wall injury. Several prospective randomized trials involving devices of this type were completed and published in 2015. In the first trial, MR CLEAN (Multicenter Randomized Clinical trial for Acute ischemic stroke in Netherlands; published in January, 2015), all cases were randomized to two groups: 233 patients who underwent endovascular mechanical thrombectomy ± standard thrombolytic therapy and 267 patients who received standard thrombolytic therapy only. The study involved patients with ischemic stroke in the anterior circulation territories; 90% of them received systemic thrombolytic therapy in both groups. The results demonstrated that favorable outcomes were significantly prevailing in the endovascular group. The percentage of outcomes with the modified Rankin scale (mRS) score being 0—2 was 32.6% in the endovascular group versus 19.1% in the control group; the mortality rate was comparable: 18.9% versus 18.4% [13].

The ESCAPE trial (Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke) involved patients with ischemic stroke in the anterior circulation territories and also compared the randomized groups: the group receiving endovascular treatment and the control group receiving systemic thrombolysis (165 and 150 patients, respectively). The therapeutic window in this study was broadened to 12 h. Patients having a large ischemic core (measured according to the perfusion CT data) or with poor collateral flow (assessed by CT angiography) were excluded from the study. Randomization was prematurely stopped as it was evident that favorable outcomes prevail in the endovascular group. The results published in February 2015 demonstrated that the percentage of patients with the outcomes assessed as 0—2 according to the modified Rankin scale was 53% and 29.3% in the endovascular and control groups, respectively. Meanwhile, the mortality rate was higher in the control group: 19.0% versus 10.6% in the endovascular group. The rates of symptomatic intracranial hemorrhage were 3.6 and 2.7% in the endovascular and control groups, respectively [14].

The EXTEND-IA trial (Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection) involving 70 randomized patients was also terminated prematurely because the endovascular treatment was evidently more clinically effective. This study involved patients with acute cerebral ischemia in the anterior circulation territory, with the volume of necrotic focus<70 ml; the therapeutic window was 6 h since symptom manifestation. The results of the study were also published in February 2018: the percentage of outcomes with mRS score 0—2 was 71% in the endovascular group and 40% in the control group of patients receiving systemic throm-
bolysis; no intergroup differences in mortality rate were observed [15].

Similar results were obtained in the industry-sponsored trial SWIFT PRIME (Solitaire FR With the Intention For Thrombectomy as Primary Treatment for Acute Ischemic Stroke), where patients were randomized to the group receiving endovascular thrombectomy using a Solitaire device and either receiving or not receiving intravenous thrombolytic therapy, as well as the group treated with systemic thrombectomy only [16].

Another trial sponsored by the manufacturer of Solitaire FR—REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) with the therapeutic window broadened to 8 h—demonstrated that favorable outcomes in the endovascular group were twice as frequent as those in the control group; no significant difference in treatment safety was reported [17].

In June 2015, in connection with the latest results of treating acute ischemic stroke, the American Stroke Association/American Heart Association (ASA/AHA) published unscheduled clinical guidelines, with endovascular mechanical thrombectomy using stent retrievers being regarded as the number one priority treatment option. Systemic thrombolytic therapy was not cancelled and was recommended to be used in combination with endovascular treatment unless contraindicated [18].

Endovascular mechanical thromboaspiration

The trend of endovascular mechanical thrombectomy using thrombus aspiration catheters was developed along with application of stent retrievers. To ensure efficacious and safe thrombus aspiration from the cerebral arteries, a catheter must possess a number of specific features that are not easily combinable in one device, namely, they need to be large-bore, have a softatraumatic distal end, being able to easily navigate in tortuous vessels and ensure sufficient proximal support. The ACE family of catheters (Penumbra, USA) has become most widely used as these catheters widely combine the properties listed above.

In June 2016, B. Lapergue et al. [19] conducted a prospective nonrandomized study and demonstrated that thromboaspiration devices are to a small extent more effective compared to application of stent retrievers.

However, a randomized prospective multicenter trial ASTER (Direct Aspiration First Pass Technique for Thrombectomy for Large Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke) [20] showed no statistically significant difference between the results of thromboaspiration and thrombectomy using a stent retriever: the revascularization rates according to the TICI (Treatment in Cerebral Ischemia) scale 2b—3 were 85.4 and 83.1%, respectively.

In actual practice, most of stroke centers employ both these methods for mechanical thrombus extraction from cerebral arteries and often combine them. The modern distal access catheters, such as Sophia (Microvention, USA) or Fargo (Balt, France), can be used simultaneously both to ensure proximal support when delivering a stent retriever and for aspiration when removing a stent retriever.

In January 2018, the American Society of Neurointerventional Surgery (SNIS) published new guidelines for treating acute ischemic stroke, with some refined information regarding combination of mechanical endovascular thrombectomy and intravenous systemic thrombolysis. TICI 2b—3 endovascular mechanical revascularization is to be the main objective of treating acute ischemic stroke. However, although systemic thrombolysis predominantly lacks effect in patients with injury in large cerebral vessels, there are no reliable data that thrombolytic therapy combined with endovascular treatment is hazardous in this case. Since there are potential chances for favorable effect of systemic thrombolysis, while being no clear evidence for its harmful effect, endovascular mechanical thrombectomy should involve intravenous administration of rtPA to patients having no contraindications for it. In its turn, systemic thrombolysis should not cause a delay in endovascular intervention [21].

Type of anesthesia and other technical intricacies of endovascular intervention

An important question related to endovascular mechanical thrombectomy is what type of anesthesia to choose. There is no consensus regarding this issue. In a number of stroke centers, these interventions are typically performed under sedation, while general anesthesia is preferred in the other ones. W. Brinjikji et al. [22] published the results of meta-analysis of 9 studies, involving a total of 1956 patients. They found sedation to be more beneficial compared to general anesthesia in terms of mortality rate and the rates of favorable outcomes and respiratory complications.

However, the randomized trial SIESTA (Sedation vs Intubation for Endovascular Stroke Treatment) [23] aiming to answer the same questions has revealed no statistically significant differences in the effect of general anesthesia and sedation.

Furthermore, the randomized trial ANSTROKE (Anesthesia During Stroke) conducted in 2017 [24] showed that the rates of favorable outcomes were equal in both groups. Hence, both types of anesthesia are acceptable and can be used in accordance with patient’s features or the protocol commonly used by the stroke team.

Using a guiding occlusion balloon catheter is another technical aspect of endovascular thrombectomy to treat patients with ischemic stroke. The devices of this type allow one to temporarily stop the antegrade blood flow at the instant of thrombus extraction, which can potentially reduce the risk of thrombus fragmentation. On the one hand, the use of guiding occlusion balloon catheters was not an obligatory criterion in the randomized multicenter studies MR CLEAN, EXTEND-IA, ES-
CAPE, SWIFT PRIME, and REVASCAT. On the other hand, there are studies demonstrating that this type of devices is safe and efficacious, while their application can reduce the time required to achieve successful revascularization of the occluded vessel territory [25].

Outside the therapeutic window

The results of randomized multicenter prospective trial DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention with Trevo) sponsored by the manufacturer of Trevo stent retrievers (Stryker, USA) were published in January 2018. This trial evaluated the potential of endovascular treatment of ischemic stroke beyond the 6-hour therapeutic window in patients for whom the severe clinical status with a relatively small size of ischemic focus was inconsistent with the time passed since symptom onset, within the time frame between 6 and 24 h by randomization. The patients were randomized to groups receiving either standard conservative treatment or endovascular thrombectomy using a Trevo device. The neuroimaging (DW-MRI or perfusion-CT) data measured to calculate the brain infarct volume were processed using RAPID automatic software (Ischemia View, USA). The results of this trial showed a significant intergroup difference in favorable outcomes. The outcome of the disease with the mRS score 0–2 was observed in 49% patients in the endovascular group and 13% of patients receiving conservative treatment. Furthermore, an analysis of the outcomes in subgroups with the 6–12 h and 12–24 h interval since the symptom onset demonstrated that the ratios between favorable outcomes in the endovascular and conservative groups were 54/19 and 43/8%, respectively [26].

Meanwhile, the results of the prospective randomized multicenter trial DEFUSE-3 conducted by the USA National Institute of Health (NIH) were published. In this trial, groups of patients receiving endovascular treatment in the therapeutic window ranging from 6 to 16 h since the symptom onset and those receiving the standard (conservative) treatment of ischemic stroke were compared. Patients were selected according to the perfusion-CT data only, with brain infarct volume <70 ml and the ratio between the volume of ischemized tissue and the ischemic core volume ≥1.8 being the inclusion criteria. These data were also calculated using the RAPID automatic software. The endovascular group showed better results, both in terms of the higher rate of favorable outcomes and lower mortality rate. The disease outcome was assessed after 3 months. The favorable outcome was observed in 45% of patients in the endovascular group and only in 17% of control group patients. The 90-day mortality rate was 14 and 16%, respectively [27].

The results of the latest randomized trials conducted in 2018 demonstrate that patient’s clinical status and neuroimaging data are more important than therapeutic time window duration and prove that endovascular mechanical thrombectomy is efficacious and safe provided that patients were properly selected during 24 h after the onset of symptoms.

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This review is devoted to recovery of blood circulation after acute ischemic stroke, with special emphasis placed on using endovascular treatment procedures. Studies focused on the procedures of systemic intravenous thrombolysis and endovascular interventions — thrombectomy and thromboaspiration — are described in chronological order. The data on the outcomes achieved by using these methods are compared. The results demonstrate convincingly that the first-generation devices used for endovascular intervention were not superior to systemic thrombolysis, while stroke outcomes have improved significantly when using the second-generation devices developed over the past decade. The authors draw a conclusion regarding the advantages of the endovascular methods to treat ischemic stroke using modern devices.

The review convincingly proves that endovascular thrombectomy is the method continuously developing due to technological advancements in the devices in accordance with relevant clinical tasks and is far from having exhausted its potential.

The reported data on stroke outcomes are impressive, but it would be appreciated if the authors had provided more information about indications for the surgery, as well as its limitations and complications. The review leaves it unclear for what stroke types this method can be used; from which arteries thrombi can be extracted; and what the structure and frequency of complications is. Without these data, one gets an impression that this method can be safely used to treat almost all stroke patients. Although it was mentioned in the review that the endovascular procedure has been included in the international recommended protocols for stroke treatment, the total number of surgeries performed so far is less than several hundreds according to the reported figures, being much lower than the incidence rate of stroke. It would be appreciated if the authors had made it clear whether this method is actually so ubiquitous in clinical practice. Russian-language publications are not cited in this review. Does it mean that thrombectomy is not used in Russia?

Overall, this review merits close attention, especially among interventional neurosurgeons and neurologists working at vascular centers and rendering urgent aid to patients with acute cerebrovascular disorders.

O.B. Belousova (Moscow, Russia)
Subarachnoid hemorrhages resulting from cerebral aneurysm rupture (aSAH) are characterized by high level of poor outcomes. Formation of delayed cerebral ischemia is one of the main causes of disability. The mechanisms underlying delayed ischemia have not yet been fully understood. Previously, the development of vasospasm was believed to be the only cause for development of delayed ischemia. In recent years, there has been evidence that hemostatic system disorders typical of this category of patients are the cause of cerebral artery thrombosis, which is one of the main pathophysiologica mechanisms for the development of delayed cerebral ischemia. This review presents an analysis of published papers on hemostasis disturbances in patients with aSAH, their pathophysiological mechanisms, and their role in the development of cerebral ischemia.

The role of the blood-brain barrier in prevention of intracranial hemorrhage

Maintenance of the balance between anticoagulants and procoagulants, as well as a fibrinolytic system, in the microcirculatory system of the brain is of great importance for normal cerebral blood flow. Under physiological conditions, anticoagulant factors and fibrinolysis dominate over procoagulant mechanisms. Hypercoagulation shift in the hemostatic system occurs in response to intracranial aneurysm rupture and facilitates formation of microthrombi [3].

The structure of the blood-brain barrier provides significant protection against hemorrhages due to the following key elements (Fig. 1):

1. Tight junction between endothelial cells characteristic of cerebral capillaries. Furthermore, the components of tight junction (transmembrane proteins claudin and occludin) form a barrier that additionally protects the brain under conditions of coagulopathies [5, 6].

2. Pericytes, which facilitate the synthesis of various trophic factors and strengthen the barrier between the brain tissue and blood [6]. It is known that pericytes have phagocytic activity against erythrocytes [7], which further strengthen the barrier. It was experimentally shown that the absence of microvascular pericytes resulted in blood-brain barrier dysfunction, activation of microglial cells, irreversible neuronal damage, and microscopic capillary hemorrhage.

3. Astrocytes, which are the main source of the tissue factor (TF) (transmembrane protein, the trigger of hemostatic system activation) in the central nervous system. Increased expression of the TF by astrocytes provides protection from hemorrhages at the microcirculatory vascular level [8]. TF can also be detected on the surface of cerebral pericytes [9].

It is recognized that TF plays the key role in the triggering of hemostatic system [10—12]. The level of TF expression differs in different organs: high levels of TF are characteristic of the brain, lungs, heart, kidneys, and placenta, while low level is characteristic of the liver, spleen, skeletal muscles, and thymus [13]. High level of TF in the brain provides additional protection from hemorrhage. Thus, the brain can initiate the hypercoagulation shift in local and systemic coagulation as a result of traumatic injury [14, 15], leading to thrombogenesis.

Hypercoagulation shift of the hemostatic system associated with aSAH

Delayed cerebral ischemia, which develops in approximately 25—35% of cases, is one of the main causes of unfavorable outcome after aSAH. This complication is one of the main causes of invalidation.

Pathophysiological mechanisms underlying delayed cerebral ischemia have not yet been fully explored. Previously, it was believed that vasospasm, i.e. narrowing of the cerebral arteries diagnosed by angiography or Doppler sonography, is the main mechanism of the development of delayed ischemia after aSAH [16].

Keywords: neurosurgical patients, subarachnoid hemorrhage, aSAH, hemostasis disturbances, microthrombosis, platelet activation, delayed cerebral ischemia, hypercoagulation, tissue factor, secondary brain injury.
In recent years, there are data indicative of the multifactorial etiology of delayed cerebral ischemia in patients with aSAH. Other pathophysiological mechanisms were considered, including formation of microthrombi in the brain vessels [16]. Aneurysm rupture is immediately followed by activation of hemostasis system. Contact between blood and TF results in rapid generation of thrombin and subsequent activation of hemostasis, whose level can be easily evaluated even in the systemic bloodstream [14]. Injury to endothelium caused by aneurysm rupture and platelet aggregation on the endothelium additionally contribute to activation of the hemostatic system [10] (Fig. 2).

Development of procoagulant activity precedes delayed cerebral ischemia [17]. F. Sehba et al. [18] experimentally studied platelet aggregation immediately after aSAH and demonstrated that increase in platelet aggregation in the cerebral vessels occurs as early as 10 minutes after the development of aSAH and somewhat decreased during the following 6 hours. Increase in thrombosis was repeatedly observed in 24 hours, which was more intensive than the previous one.

S. Stein et al. [19] examined the presence of microthrombi in cerebral regions supplied by the anterior cerebral, posterior cerebral, and middle cerebral arteries (girva, hippocampus, and insula) during aSAH obtained by autopsy of 29 patients after aSAH. The authors demonstrated that formation of microthrombi along with vasospasm underlie the development of ischemic foci. There was a significant correlation between microthrombosis and delayed cerebral ischemia. Significantly higher number of microthrombi (10.0/cm²) was found in patients with clinical and morphological signs of delayed cerebral ischemia, and significantly lower (2.8/cm²) — in patients without ischemic lesions. Staging of thrombosis was also observed. Peaks occurred on day 1—2 after the hemorrhage and were characterized by a particularly intense thrombosis. On days 3 and 4, there was a tendency to regression. In the cases with development of delayed ischemia, the intensity of thrombosis increased again at the end of the first week and remained high until the end of the second week. In contrast to this situation, the level of thrombosis was quite low in patients who died without the development of delayed ischemia.

S. Juvela et al. [20] assessed platelet aggregation induced by adenosine diphosphate and associated thromboxane B2 secretion in 52 patients with aSAH to find a possible relationship between increased activity of platelet function and the development of cerebral ischemic complications after aSAH. Significant increase in platelet activity and thromboxane secretion was observed 1—2 weeks after hemorrhage.

The highest values of thromboxane secretion were observed in patients with clinical and radiological signs of delayed cerebral ischemia. Increase in the level of systemic inflammatory markers, such as interleukin (IL)-6 and beta-IL-1 in blood samples obtained from the internal jugular vein of patients, as well as increase in the level of platelet activating factor, strongly affecting aggregation of platelets, were observed on day 4—14 after hemorrhage. Its level was proven to increase under conditions of ischemia. Additionally, it was found in experimental models that its systemic administration reduced microcirculation [21].

In 2017, J. Frontera et al. [22] investigated activity of platelet function using the thromboelastographic index, as well as the dynamics of C-reactive protein in 106 patients with aSAH. Both values increased within 72 hours after aSAH. There was a correlation between increase in these values and the severity of patients’ condition as assessed by the Hunt–Hess score; in patients with delayed cerebral ischemia, platelet activity was significantly higher than in patients without neurological deficit. The authors analyzed the 3-month period after aSAH and concluded that activity of platelets was significantly higher in patients with lethal outcome and disability.

There are also studies discussing other possible mechanisms of hypercoagulation shift in the hemostatic system after aSAH. Vasopressin receptor V1a widely occurs in the brain (for example, on the surface of endothelial cells) [23]. Interaction between vasopressin and V1a receptor facilitates platelet aggregation and vasoconstriction [24]. Z. Liu et al. [25] studied the dynamics of expression of vasopressin receptor V1a and its possible effect on platelet aggregation in the experimental models of aSAH. The authors showed that the level of vasopressin rapidly increased 6 and 24 h after hemorrhage. Expression of integrin GPIIb/IIIa (glycoprotein located on the platelet membrane used to determine platelet aggregation) peaked in the cortex and hippocampus within 24 hours after aSAH. The immunofluorescence method showed that vasopressin and integrin GPIIb/IIIa have the same localization and thus demonstrated stimulation of platelet aggregation with vasopressin. It was shown that high...
plasma level of vasopressin correlates with secondary brain damage after experimental aSAH [26].

In 2016, P. Foreman et al. [27] examined 156 patients with aSAH and demonstrated a correlation between the development of nosocomial infection and delayed cerebral ischemia. According to the authors, nosocomial infection enhances the systemic inflammatory response, which causes the development of thrombosis and subsequent ischemia in patients with aSAH. According to M. Levi et al. [28], infection results in secretion of plasminogen activators (t-PA and U-PA), which are neutralized by the inhibitor of type 1 plasminogen activator (PAI-1), which leads to complete inhibition of the fibrinolysis process and, as a consequence, insufficiently effective removal of fibrin and development of microvascular thrombosis. Some pro-inflammatory cytokines (IL-1, IL-6, and IL-8) are associated with the development of vasospasm and secondary cerebral ischemia. Pathophysiological mechanisms, through which cytokines lead to ischemia, are poorly understood. It is known that IL-6 has vasoconstrictive properties in vitro [29]. According to C. McMahon et al. [30], leukocytosis and changes in the level of IL-6 can be regarded as a predictor of secondary cerebral ischemia. There are numerous data that inflammatory reactions activate the hemostatic system and suppress anticoagulant mechanisms [28]. Therefore, systemic inflammatory reactions in patients with aSAH can further enhance hypercoagulation shift, leading to microthrombosis and secondary cerebral ischemia.

Ettinger [cited in 31] demonstrated a correlation between elevated fibrinogen levels and the risk of lethal outcome. Other researchers have showed that elevated levels of fibrinogen, D-dimer, and thrombin-antithrombin complex may serve as predictors of delayed cerebral ischemia after aSAH.

In experimental models, intracranial aneurysm rupture leads to increase in intracranial pressure and, as a consequence, hypoperfusion [32, 33]. Reduction of cerebral blood circulation initiates a cascade of reactions involving platelet activation and inflammation, which leads to formation of microthrombi, ischemia, vasogenic edema, and early brain damage [18, 34, 35]. Activation of platelets further enhances the inflammatory cascade [36]. Activated platelets and inflammatory cytokines further affect the endothelium, enhancing formation of microthrombi and inflammation [18, 35, 37, 38].

Since activation of the hemostatic system in patients with aSAH can lead to formation of microthrombi and cause secondary cerebral ischemia, increasingly more attention is paid to therapy aimed at reducing platelet activation. S. Dorhout Mees et al. [39] conducted a meta-analysis of 5 studies on the use of antiplatelet agents in patients with aSAH, which included 669 patients. The study showed that the use of antiplatelet agents reduces
the risk of delayed cerebral ischemia by 15%, while the risk of hemorrhagic disorders insignificantly increased. Nevertheless, there are no recommendations on the use of antiplatelet agents in patients with aSAH [40].

The study of the effect of therapy with low-molecular-weight heparins led to controversial results. J. S. iqren et al. [41] assessed the effect of sodium enoxaparin in 170 patients with aSAH in a double-blind, randomized clinical trial. In the study group, enoxaparin (single dose of 40 mg) was administered on the following day after aneurysm occlusion, provided that the operation was carried out within 48 hours after aSAH and intracranial hematoma did not exceed 20 mm in diameter at the first postoperative CT examination. The duration of therapy was 10 days. The result was assessed in 3 months using the Glasgow outcome scale and modified Rankin scale. The authors demonstrated that no significant difference in the results of treatment was observed in 3 months. Lethal outcome was observed in 6% of cases, and only 95 (56%) out of 170 patients demonstrated good effect of therapy. The authors concluded that the use of low-molecular-weight heparins should be possibly avoided in view of the increased risk of hemorrhagic complications and the absence of influence on neurological outcomes in patients with aSAH.

Antifibrinolytic therapy (for example, tranexamic acid) can reduce the probability of re-hemorrhage. At the same time, Roos et al. [42], who analyzed the course of the disease in 1399 patients with aSAH, concluded that treatment with antifibrinolytics is associated with increased risk of delayed cerebral ischemia. These data discourage the routine use of antifibrinolytics in treatment of patients in the acute period of aSAH.

**Conclusion**

Maintaining the balance between anticoagulants and procoagulants, as well as the fibrinolytic system, in the microcirculatory system of the brain is of great importance for normal cerebral blood flow. It was proved that formation of microthrombi along with the development of vasospasm forms the basis for the development of ischemic foci. At the same time, the mechanism of their formation is not fully understood, and therefore the study of the pathophysiological mechanisms that underlie the phenomenon of hypercoagulation shift of the hemostatic system after aSAH is increasingly more important.

Authors declare no conflict of interest.

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Despite the fact that the practice of intensive therapy for SAH is to a certain degree protocol-based, it still has many white spots. In this literature review, the authors raised the problem of ischemic complications, which are the main cause of disability. In addition to traditional understanding of the mechanism of formation of microaggregates and thrombosis as a result of increased resistance in the capillary pial system of the distal parts of the vascular bed narrowed due to vasospasm, the authors drew attention to the role of changes in the local and general hemostatic system. Systemic inflammatory response, neuroendocrine changes, substances associated with endothelial damage, increase in local concentration of tissue thromboplastin during sympathetic “storm” — all of these lead to an increase in platelet aggregation activity with subsequent ischemic events. The relationship between platelet activity and the risk of ischemic disorders as shown by thromboelastogram was first discovered by the authors in recent publications. New data that increase in plasma vasopressin level correlates with secondary brain damage was also unexpected. News about hemostasis associated with aSAH do not enable adjusting the pharmacotherapy protocol, but they provide arguments to explain the development of ischemia in the cases with unobvious decrease in blood flow (according to CT perfusion). I agree with the authors that it would be a good idea to mention the antiaggregant therapy in the guidelines (although it is widely used off-label), but I disagree with them for no more than 72 hours in cases of delay in the treatment. I think that the article is highly interesting and relevant for understanding of the complexity of intensive therapy of non-traumatic SAH, especially for neurosurgeons.
Commentary

The state of hemostatic system is highly important for any surgical patient, but it is especially important for patients with cerebral pathology. The relevance of this problem is evidenced by rather high number of reviews published in top ranked neurosurgical and other journals in the last year [1—5], and even the manual on this issue [6]. Aneurysmal SAH (aSAH) does remains a serious problem in neurosurgery. It is clear that blood outflow from the bloodstream necessarily causes changes in the hemostatic system, at least local ones, at the site of hemorrhage, but possibly also at the systemic level [7, 8]. In my opinion, the mere fact that the authors focused on hemostatic disorders associated with aSAH, which are not often discussed in the Russian journals, is undoubtedly the merit of the authors. However, let us discuss the study itself.

The fact that the article is a literature review becomes apparent only from the introduction.

The article starts with the chapter “The role of the blood-brain barrier in prevention of intracranial hemorrhages”, which is, in general, a detail question of such an extensive problem addressed by the authors. I would start with more important and interesting systemic shifts. However, this is not the main thing, since everybody of us understands any problem in his/her own way. However, the authors describe the organization of the blood-brain barrier in two pages, although there is a lot of information and even decent books on this topic [9]. The authors discuss only some aspects of this extremely complicated system, focusing on tight junction between endothelial cells, pericytes, and astrocytes. Here, the key concept of tissue factor (TF) is for the first time mentioned in the text, however, without special explanation of its essence, although it deserves explanation. This is a special type of cytokine receptors, specifically binding the complex of factors VII/VIIa and playing a key role in the processes of hemostasis, thrombosis, inflammation, angiogenesis, and tumor growth [10].

It is well known that the brain substance is exceptionally rich in various procoagulants [2, 11]. Inflow of these procoagulants into the systemic bloodstream may be important in the case of brain injury, but it is not entirely clear, what this has to do with the situation of aSAH.

The next section, and it is the last one, is titled “Hypercoagulation shift of the hemostatic system in patients with aSAH”. In fact, this section provides almost no information about systemic hemostatic disorders. The reader is provided with information on the overall mortality associated with aSAH and the incidence of delayed ischemia, as well as the lack of knowledge of its mechanisms. Then the authors proceed with idea of microthrombosis in the microcirculatory bed of the brain. The idea of microthrombi is beautiful, but stop — it is not a systemic shift! Then why is this information provided?

Next, there is information from various relatively old publications (10, 15, and even 27 years ago) on the morphology of microthrombosis and systemic hemostatic changes in the form of increased platelet aggregation. The results of a recent study in 2017, where platelet function was assessed with thromboelastography, are presented in support of the latter thesis. However, it is known that thromboelastography is not an optimal method for evaluation of platelet function and other techniques are more appropriate for this purpose [1, 4, 12]. I think that a lot of people will agree with me that all this looks very questionable. But here the authors flood a reader with three consecutive very complex blocks of information.

The first one is about the expression of receptors of vasopressin (V1a) and integrin (GPII/IIIa) in the brain. But, have mercy, all the data of this chapter were obtained only in experiments on laboratory animals, without clinical confirmation, and it is absolutely unclear why they are given a place in the discussion of systemic hemostatic shifts in patients with aSAH.

The second block is about inflammation and hemostasis. Again, it is well known that any inflammatory process activates the hemostatic system, and first of all its procoagulant element at the local and sometimes systemic level. There are enough publications on this topic [13—16]. The question is, how important is the role of this inflammatory activation of the hemostatic system in the genesis of its systemic disorders? I think this role is not so obvious.

And the third block. Aneurysmal SAH causes increase in intracranial pressure, decrease in cerebral perfusion, and, as a result, activation of platelets! And the latter, of course, again contribute to formation of microthrombi in microvessels.

In general, it turns out that everything that happens in the body of a patient with aSAH leads to thrombosis and a poor outcome. Probably, so it is. But what should we do? And the last page of the review focuses on actions. The idea is clear: these ill-fated activated platelets should be deactivated, since they are harmful. And here they are, actions. The use of disaggregants in patients with aSAH reduces the incidence of delayed ischemia by 15% [17]. This is a meta-analysis, and the work was published 15 (!) years ago (although in a respected journal (Stroke)) and had no clinical consequences, and, as the authors rightly point out, this therapy was not included in treatment protocols for patients with aSAH. Furthermore, the use of low-molecular-weight heparins in the postoperative period in patients who had aSAH did not change the statistics of neurological outcomes [18]. At the same time, as the prof. A.A. Belkin (the first commentator) wrote, inhibitors of fibrinolysis were included in the protocol and this was supported by a solid evidence base, especially with regard to prevention of repeated hemorrhage within the first 6 hours [19, 20]. However, from the viewpoint of the discussed problem of hemostatic disorders, it
is important that none of the studies showed worsening of treatment outcomes associated with administration of fibrinolysis inhibitors.

In summary, this article provided me only with the following information. There is a morphologically described phenomenon of the presence of microthrombi in the microvascular bed of the brain after SAH, but it is not entirely clear when they were formed and what role they played. It is fairly possible that this is only a part of the universal sanogenic mechanism of cerebral injury. And I suspect that such a morphological picture can be detected in all the main types of cerebral lesions, including traumatic injury, CNS tumors, cerebral circulation disorders [21, 22, 24, 25]. But the main point is that, in my opinion, no changes in the therapy of these patients (with aSAH) can be made based on the information provided in this literature review. However, the authors of the review do not insist on this. However, this is not for the first time. Thus, one of the recent reviews on a similar topic published this year also provides no therapeutic recommendations and concludes that “further research is required” [13].

Once again, the problem raised by the authors is interesting itself, but I was not convinced by the article.

And one more remark. The study carried out by 9 authors consists of 4 pages of journal text, not including the reference, and 2 illustrations. This is an average of half a page per author. Not very much. But the creative process is individual: somebody writes alone, and someone needs a large team of authors. However, there is a section “Personal contribution of the author” in some journals. Just by the way.

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