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In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the Problems of Neurosurgery named after N.N. Burdenko was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.

Topics to be covered in our next issue

- Stereotactic radiosurgery in treatment of trigeminal neuralgia
- Neurostimulation for critical low limb ischemia
- Treatment of uncomplicated vertebral compression fractures
The development of post-traumatic hydrocephalus (PTH) after severe traumatic brain injury can cause, in some cases, severe impairment of consciousness and prevent rehabilitation of patients. The influence of cerebrospinal fluid (CSF) circulation disorders on processes of consciousness recovery is a fundamental problem that requires in-depth research. The issues of differential diagnosis, results of surgical treatment of PTH, and its complications in patients in the vegetative status (VS) and minimally conscious state (MCS) remain poorly covered.

**Material and methods.** We performed a retrospective analysis of the long-term outcomes of surgical treatment in 82 PTH patients in the VS (38 cases) and MCS (44 cases).

**Results.** A significant clinical improvement occurred in 60.6% of VS patients and in 65.9% of MCS patients. The rate of shunt infection was high and amounted to 21.05% in the group of VS patients and 20.4% in the group of MCS patients. The rate of shunt system dysfunction was 26.05% in the first group and 20.4% in the second group. Postoperative mortality (associated directly with treatment complications) was 3.6%. Total mortality was 10.9%.

**Discussion.** The positive effect of shunting surgery in patients with gross impairment of consciousness was associated with transition to higher levels of consciousness. The high rate of complications, especially infections, was due to a serious condition of patients and comorbidities, in particular chronic infection foci. Shunt system dysfunction was not a factor of the adverse outcome of surgical treatment because rarely led to irreversible consequences, but required repeated surgery. Mortality after shunting surgery was significantly higher in patients with gross impairment of consciousness than in other groups of patients. We found a correlation between deaths in VS patients and shunt infection in the postoperative period.

**Conclusion.** CSF shunting surgery is an important step in surgical rehabilitation of PTH patients. To assess the contribution of various risk factors to the development of shunt infection and to develop measures reducing its rate, further prospective studies are needed.

**Keywords:** traumatic brain injury consequences, post-traumatic hydrocephalus, shunting surgery, consciousness recovery, vegetative status, minimally conscious state, shunt infection.

**Abbreviations:**
- TBI — traumatic brain injury
- PTH — posttraumatic hydrocephalus
- VS — vegetative status
- MCS — minimally conscious state
- CT — computed tomography
- MRI — magnetic resonance imaging
- CSH — chronic subdural hematoma
- DAP — diffuse axonal injury
- PE — pulmonary embolism

Introduction of evidence-based guidelines for the management of severe TBI into clinical practice improved the outcomes in these patients [1—3]. However, the result of this tendency is increased number of patients with consequences of TBI that has become a socially significant and common problem in neurosurgery, neurology, psychiatry and adjacent specialties [4—6]. There are over 2 million disabled people with consequences of TBI in Russia and over 5 millions in the USA [7, 8]. Moreover, there are about 35 thousands patients in VS and about 280 thousands in MCS in the USA. The cost of rehabilitation for the entire life varies from $600 thousands to $1.85 million per one patient [9].

Research of consciousness recovery in patients after severe TBI is a fundamental problem. Getting out of coma and stages of consciousness recovery are described both in Russian [10, 11] and foreign literature [12—14]. B. Jennet and F. Plum described and introduced the concept of “persistent vegetative status” in 1972 [15]. This conception was further elaborated by the International Working Party — Report on the Vegetative State group [16]. The following criteria for the diagnosis of “vegetative status” were proposed:

- no patient’s awareness himself and environment;
- no mental response to various external stimuli;
- no signs of speech comprehension or attempts to speech;
- function of autonomic nervous system sufficient to maintain vital activity with adequate care;
- no control over pelvic organ function;
- episodes of awakening (arousal), appearance of sleep-wakefulness cycle;
- intact cranial nerve reflexes and/or spinal reflexes.

Aspen Workgroup developed the concept of “minimally conscious state” [17]. MCS diagnosis is based on one or more criteria:
— performance of elementary instructions;
— answers the questions: “yes”/“no” (both verbal and non-verbal);
— articulation or attempts to speech;
— emotional or targeted motor activity:
— visual gaze fixation;
— crying, laughing, smiling in response to speech, images, music, etc.;
— speech or articulation in response to the questions;
— attempts to use surrounding objects (comb, pen, etc.).

MCS includes akinetic or hyperkinetic mutism, mutism with emotional reactions and mutism with speech comprehension [18].

According to CT or MRI data, ventriculomegaly is more common in patients with consequences of TBI in VS and MCS [19, 20]. Differential diagnosis of ventriculomegaly as a result of atrophy and true hydrocephalus in victims with TBI is still unclear [21—23].

True PTH often remains undiagnosed, and, conversely, unreasonable bypass procedures are performed in patients with atrophic ventriculomegaly. A. Marmarou et al. [21] reported post-traumatic ventriculomegaly in 33 (44%) out of 75 patients with severe TBI. Liquorody- namic disorders associated with PTH were verified only in 15 (20%) cases. Absence of non-invasive and sensitive diagnostic methods impedes differential diagnosis of these conditions.

PTH is often observed already in subacute period of TBI and can prevent recovery of consciousness [11, 19, 20, 24—26].

Patients in VS and MCS are the most difficult regarding differential diagnosis and determination of indications for surgical treatment. Only 5 articles were found in the Medline database using keywords “posttraumatic hydrocephalus (AND) mental recovery (OR) vegetative state (OR) minimal consciousness state”. It is worth to note that patients in VS and MCS were only a part of the group and were not separately considered in detail in all trials.

Time of bypass surgery after severe TBI and its influence on mental recovery rate is still unclear [24, 26].

Patients with PTH and impaired consciousness due to comorbidities and chronic focal infection (tracheostomy, gastrostomy, bedsores) are vulnerable to complications even after minimally invasive diagnostic procedures. Cerebrospinal fluid drainage may be a trigger for decompensation of water-electrolyte balance, hormonal disorders, exacerbation of chronic infection and even the development of meningitis.

The purpose of this retrospective study is to analyze the effect of CSF-shunting surgery on mental recovery and the role of various factors potentially influencing outcomes in patients in VS and MCS after severe TBI.

Material and methods

There were 210 patients (163 men (77.6%) and 47 women (22.4%), mean age 31.6±15.7 years) who underwent surgery for PTH in the Burdenko Neurosurgery Center in 1986—2016.

This analysis included 82 (39.1%) patients with severe impairment of consciousness as a leading clinical manifestation of TBI. Group 1 included 38 (18.1%) patients in VS, group 2 — 44 (20.9%) patients in MCS. All patients suffered severe TBI. The main characteristics of both groups are presented in Table 1. The median of the period from injury to bypass surgery was 4 months (range 1—28.5 months).

Primary preoperative examination was carried out according to a standard protocol and included clinical examination, CT and/or MRI. Indications for surgery were determined by improvement of mental status after lumbar puncture followed by drainage of 40—60 ml of CSF (lumbar tap-test). Advanced bulging of soft tissues within cranial defect justified liquor bypass surgery for severe hypertensive hydrocephalus. In our study, consciousness level was assessed in accordance with stages of consciousness recovery in patients after prolonged coma (Table 2).

These stages are accepted in our clinic to determine the level of consciousness in patients with consequences of TBI. They are easy to be interpreted and may be identified by neurosurgeon or resuscitator at the patient’s bedside without application of additional neuropsychological and psychopathological tests as a rule.

Distribution of patients in the 2nd group according to the stages of consciousness recovery after prolonged coma until surgical treatment is presented in Table 3.

There were 82 CSF-shunting procedures including ventriculoperitoneostomy (n=78), ventriculostrooysteria (n=3) and lumboperitoneostomy (n=1). Surgical interventions were performed in standard fashion. Ventriculoatriosy was applied in patients after previous abdominal surgery and suspected adhesions in abdominal cavity. Lumboperitoneostomy was performed in a patient with slit-like ventricles and hydrocephalus followed by bilateral subdural hygromas.

Database was collected using Microsoft Excel software. Statistical analysis of data was performed using R (version 3.3.2, www. R-project.org) and IDE R Studio (version 1.0.136) software package. Fisher’s exact test was used to assess differences between categorical variables (considering small sample size), Mann-Whitney test — for ordinal variables. Spearman correlation coefficient was applied for analysis of quantitative variables. Differences were significant at p-value<0.05.

Sixty-one (74.4%) out of 82 patients underwent craniectomy in acute period of injury. Cranioplasty after drainage procedure was performed in 39 patients. In total, there were 249 operations considering decompressive procedures in acute period of injury and 67 redo inter-
Interventions for various complications. All patients with skull defects underwent bypass surgery prior to cranioplasty. Positive postoperative changes in neurological status were observed in 52 (63.4%) out of 82 patients, 30 (36.6%) patients had no clear clinical effect. Postoperative improvement of consciousness up to mutism with speech comprehension or higher was considered as a positive result of treatment in the 1st group. This state was determined as essential since it implies minimal contact and performance of the elementary instructions. Positive results were noted in 23 (60.6%) out of 38 patients (Fig. 1). None of patients has reached the highest stages of mental status recovery and premorbid level although recovery of complete and correct orientation with certain manifestations of psychoorganic syndrome was observed in 8 (21.05%) patients.

Complications of CSF-shunting procedures

Graft-infection complicated postoperative period in 17 (20.7%) out of 82 patients that required 45 additional interventions including external deployment of distal catheter, implantation and reimplantation of external ventricular drainage tubes and/or reimplantation of shunts. Basal liquorrhea in long-term period after TBI was significantly associated with advanced risk of infectious events ($p=0.041$) in contrast to wound or basal liquorrhea, meningitis or local wound infection in acute period of injury.

Different types of inadequate drainage of cerebrospinal fluid due to dysfunction and hyperfunction of shunts were noted in 19 (23.4%) victims. Inadequate drainage of cerebrospinal fluid was combined with infectious complications in 6 (31.6%) cases. There were 22 redo procedures in 9 out of 13 (68.4%) patients without infection. Other 4 patients required correction of shunt’s function via reprogramming valve opening pressure.

Intracranial hemorrhagic complications were noted only in 3 cases in the 1st group. In the first case, intraventricular hemorrhage occurred after removal of ventricular catheter of due to infection. Adequate therapy and CSF sanation were followed by reimplantation of bypass system. However, patient died after 8 months due to pulmonary embolism. Intracerebral hematoma along the ventricular catheter was confirmed by postoperative CT in

---

Table 1. Main demographic and epidemiological data of patients with PTH in VS and MCS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (VS)</th>
<th>Group 2 (MCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Median of age, years</td>
<td>36.2</td>
<td>31.6</td>
</tr>
<tr>
<td>Gender, m/f</td>
<td>30/8</td>
<td>32/12</td>
</tr>
<tr>
<td>Mean time from TBI to bypass procedure</td>
<td>5.6</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Table 2. Stages of consciousness and mental activity recovery in patients after prolonged coma (T.A.Dobrokhotova et al., 1985; O.S.Zaitsev, 1993) [10, 11, 24, 27]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms of mental recovery</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No</td>
<td>Coma</td>
</tr>
<tr>
<td>I</td>
<td>Eye opening</td>
<td>Vegetative status</td>
</tr>
<tr>
<td>II</td>
<td>Visual gaze fixation</td>
<td>Akinetic mutism without emotional reactions</td>
</tr>
<tr>
<td>III</td>
<td>Differentiated emotional reactions</td>
<td>Akinetic mutism with emotional reactions</td>
</tr>
<tr>
<td>IV</td>
<td>Speech comprehension</td>
<td>Mutism with speech comprehension</td>
</tr>
<tr>
<td>V</td>
<td>Attempts to speak</td>
<td>Speech disintegration</td>
</tr>
<tr>
<td>VI</td>
<td>Answers the questions</td>
<td>Amnestic confusion</td>
</tr>
<tr>
<td>VII</td>
<td>Environmental orientation</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>VIII</td>
<td>Efficiency of cognitive processes</td>
<td>Psychopathy-like syndrome</td>
</tr>
<tr>
<td>IX</td>
<td>Adequacy of emotional and personal reactions</td>
<td>Neurosis-like syndrome</td>
</tr>
<tr>
<td>X</td>
<td>Premorbid mental adaptation</td>
<td>Premorbid mental level</td>
</tr>
</tbody>
</table>

Table 3. Preoperative distribution of patients in the 2nd group by the stages of consciousness recovery after prolonged coma

<table>
<thead>
<tr>
<th>Consciousness level according to the stages of mental recovery after prolonged coma</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinetic mutism</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Akinetic mutism with emotional reactions</td>
<td>10</td>
<td>22.7</td>
</tr>
<tr>
<td>Mutism with speech comprehension/MCS plus&lt;</td>
<td>23</td>
<td>52.3</td>
</tr>
<tr>
<td>In all</td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
</table>
the second case. Complete resorption of the hematoma was further observed but bypass surgery did not lead to significant clinical improvement. Bilateral chronic subdural hematomas without any neurological symptoms were diagnosed during control MRI in the third case. Replacement of bypass system valve and closed external drainage of hematomas were not associated with significant neurological changes. Structure of complications and their incidence are summarized in Table 4. Age, injury mechanism and malfunction of drainage system did not significantly influence the outcomes of bypass surgery.

Infection-related mortality after CSF-shunting procedures was 4.8% (n=4) among patients in VS within 4.5—11 months after primary or redo intervention (Table 5).

In 3 VS patients and 2 MCS patients, lethal outcomes within 2.5—24 months were due to extracranial complications (pneumonia complicated by sepsis (n=3), pulmonary embolism (n=2)). Mortality rate was similar in both groups (p=0.074).

Postoperative shunt-infection correlated with mortality in group 1 (Table 6).
Clinical observation

A 32-year-old patient gets injured on 09/25/16 by the fragment of grinding stone in the frontal area along the midline. Patient was taken to the regional hospital in unconscious state. Craniotomy and removal of hematoma and free osseous fragments were performed (Fig. 3).

Duration of coma was unknown from medical records. According to relatives, VS developed after 14 days and was associated with severe tetra-syndrome, vegetative crises manifested by tachycardia, tachypnea, fever and diffuse muscle hypertonicity. The patient was hospitalized to the Burdenko Neurosurgery Center in 1.5 months after injury in VS with severe tetra-syndrome. There were CT — and MR-signs of ventriculomegaly (Fig. 4). Lumbar drainage (tap-test) was followed by improved consciousness, signs of speech comprehension, response to basic instructions. However, bypass surgery using a programmable valve was performed only in 5 months after TBI due to chronic catheter-associated urinary infection and need for therapy. Postoperative CT confirmed correct position of ventricular catheter and reduced ventricular system (Fig. 5a).

Ventriculoperitoneal bypass was followed by significant positive changes: patient followed the doctor’s instructions after 7 days (raised and shook hands, took the bottle of water, brought it to his mouth and independently drank). Attempts to speak occurred after 3 weeks. The next stage of treatment was skull defect repair with polymethylmethacrylate and preliminary stereolithographic modeling (Fig. 5b). Control examination in 11 months after ventriculoperitoneal bypass surgery and 10 months after skull repair revealed recovery of orientation in personal situation, place and time. Mental retardation and tetraparesis persisted but patient fully served himself in everyday life.

Discussion

Critical illness of victims with TBI, foci of chronic infection, uncertain rehabilitation prognosis and risk of various complications may limit the indications for bypass system implantation in patients with signs of post-traumatic hydrocephalus in VS or MCS. Nevertheless, our experience over the recent years, as well as reports of other authors indicate that even in some of these patients CSF-shunting surgery is able to restore consciousness and significantly improve social adaptation [11, 19, 20, 24, 29, 30].

The main result of this study is favorable clinical effect of bypass surgery in 52 (63.4%) out of 82 patients with post-traumatic hydrocephalus in VS or MCS. At the
same time, recovery of consciousness was noted in 23 (60.6%) out of 38 patients in the 1st group and in 29 (65.4%) out of 44 patients in the 2nd group. However, in our sample, bypass procedure was not followed by clear clinical effect in 30 (36.6%) patients despite obvious post-traumatic hydrocephalus. Probably, impaired consciousness in some of these patients was caused by not only post-traumatic hydrocephalus, but also severe primary and secondary damage of brain stem and subcortical structures. This is evidenced by MRI data in patients with severe TBI [31–34]. Correlation of the level of damage with the results of bypass surgery in patients with PTH is a subject for further research.

Limitations of our study are retrospective design and various follow-up periods (range 1—13 years, median 7 years). However, it is known that recovery of consciousness and other cerebral functions may be observed also in long-term period after TBI [35, 36].
According to some authors, development of hydrocephalus within 6 months after TBI prevents recovery of consciousness and mental activity while hydrocephalus in delayed period aggravates neurological deficit [11, 24, 27—29]. We indirectly assessed correlation of duration of hydrocephalus and the outcomes in our study considering period between TBI and bypass surgery. R. Kowalski et al. used the same approach in the recent research [26]. There was no correlation between the dates of bypass surgery after TBI and the outcomes in our sample. Probably, this is due delayed surgery in both groups (median 4 months). Only 9 out of 82 patients underwent surgery later than 12 months after injury. R. Kowalski et al. reported improved rehabilitation prognosis in patients with PTH undergoing early bypass procedure (up to 69 days after TBI) [26]. It is also interesting to determine the critical period from the moment of PTH occurrence to surgery that would be followed by mental recovery and neurological improvement [28, 29].

According to the literature, incidence of shunt-infection in the treatment of various forms of hydrocephalus is 1—15% [28, 29, 37—40]. Local chronic infection is a risk factor for inflammatory complications after bypass surgery. However, prospective trial is required to assess the role of various predictors of infection in the treatment of patients with PTH. In our study, 34 (89.5%) patients in the 1st group and 34 (77.3%) patients in the 2nd group had bedsores, tracheostomy, gastrostomy or their combination.

Shunt-infection was observed in 8 (21.05%) patients of the 1st group and in 9 (20.4%) patients of the 2nd group. Shunt-infection resulted death in 50% of case in the 1st group. Favorable outcomes were observed in 3 cases. There were no any changes in consciousness in another case. In the 2nd group, all 9 cases of shunt-infection were successfully cured. However, meningeoencephalitis and ventriculitis resulted VS in 2 patients.

Incidence of drainage system dysfunction followed by syndromes of inadequate CSF outflow was similar in both groups (26.3 vs. 20.4%). There was no correlation between drainage system dysfunction and the outcome in both groups. This is probably due to the reversibility of CSF passage disorders after correction of inadequate drainage.

According to the literature [40–42], mortality rate after CSF-shunting procedures in patients with hydrocephalus is usually low (1.4—2%). We did not find accurate data about mortality in large-sample reports devoted to surgical treatment of PTH in patients in VS or MCS. In this study, outcomes were assessed within different follow-up periods (1—13 years). Comprehensive analysis revealed that lethal outcomes were usually caused by decompensation of chronic diseases in long-term period after surgery rather surgical treatment per se. Five (6.1%) patients died within 2—24 months due to generalization of focal infection and thromboembolic complications. Mortality associated with complications of surgical treatment was noted only in patients with VS including 3 deaths due to shunt-infection. Another patient died in 18 months after bypass surgery due to skin failure within skull defect followed by drainage system infection. Thus, mortality rate directly related to CSF-shunting surgery was 4.8%. This value is significantly higher than that in
patients with hydrocephalus of other genesis and no severe concomitant diseases and chronic infection.

**Conclusion**

Thus, correction of CSF circulation in patients with VS and MCS can significantly improve rehabilitation prognosis and facilitates recovery of consciousness. CSF-shunting surgery with cranioplasty may be considered as necessary stages of surgical rehabilitation of patients. Nevertheless, incidence of unsatisfactory outcomes remains high. Therefore, development of diagnostic predictors of an unfavorable prognosis for the treatment of post-traumatic hydrocephalus in patients with severe impairment of consciousness is necessary. Perhaps, modern MRI modalities will be valuable to visualize injury of deep cerebral structures which are important for recovery of consciousness [43, 44].

Comorbidities and chronic infection predispose to complications of CSF-shunting surgery that is evidenced by the high incidence of shunt-infection. Shunt-infection in patients with post-traumatic hydrocephalus in vegetative status is an adverse prognostic factor. Prospective studies are required to assess the influence of various risk factors on the development of shunt-infection.

Authors declare no conflict of interest.
The article of professor A.D. Kravchuk et al. is devoted to a very important neurosurgical problem — treatment of hydrocephalus in patients with VS and MCS. These patients are usually missed by neurosurgeons primarily due to severe neurological deficit and critical condition caused by not only hydrocephalus per se but also comorbidities, post-traumatic complications, chronic infection, etc. The problem is undoubtedly relevant due to supposed neurosurgical care in victims with severe TBI. Authors’ data confirm that correction of CSF circulation in patients with VS and MCS can significantly improve rehabilitation prognosis and facilitates recovery of consciousness. In particular, the authors noted significant clinical improvement in 60% of patients in vegetative status and in 66% of those in MCS. Of course, incidence of shunt-infection (21%) and drainage system dysfunction (23.5%) was high. However, this fact is certainly associated with comorbidities and only once again emphasizes difficult treatment of these patients. Overall and postoperative mortality was 11 and 3.6%, respectively. According to the literature, these values are significantly higher than in patients with hydrocephalus of another etiology. However, the authors have found that mortality (8.5%) was predominantly presented by patients in more severe condition. The authors have also demonstrated correlation between mortality in patients with VS and postoperative shunt-infection that is again associated with severity of patients’ condition. The authors did a tremendous work and confirmed that CSF-shunting surgery is followed by recovery of consciousness in some patients and improved subsequent adaptation. In conclusion, I would like to note high methodological level of research and qualitative illustration of clinical observation. Complex issues of diagnosis and treatment of patients in VS and MCS are comprehensively described. The article demonstrates high significance of the results and will be interesting for neurosurgeons and neurologists, teachers, postgraduate students and residents of medical universities.

G.V. Gavrilov (St. Petersburg, Russia)
The article is devoted to an actual medical problem — treatment of post-traumatic hydrocephalus in patients with severe impairment of consciousness. To date, the criteria for CSF-shunting procedures in patients with TBI, subarachnoid hemorrhage and brain tumors are well known and described. However, there are very few foreign and national reports devoted to surgical treatment of the most difficult and seemingly hopeless group of patients with MCS. There are no randomized trials devoted to this problem. Surgical experience of interventions in patients with VS, post-traumatic hydrocephalus and skull bone defect is limited and presented by only a few cases even among the most famous surgeons. Nevertheless, CSF-shunting surgery and cranioplasty may be necessary stages in surgical rehabilitation of patients. Risk of suppurative complications in critically ill patients with multiple organ failure may be a contraindication for these procedures.

The authors present their experience of these operations at the Center for Neurosurgery. Retrospective analysis included 82 patients with post-traumatic hydrocephalus in vegetative state and minimal consciousness state. Types of post-traumatic disorders of consciousness, indications for surgery, types of interventions, outcomes and complications are described. Statistical analysis of the data was also carried out. Comparison of similar pre- and postoperative diagnostic methods and analysis of ventriculocranial coefficients before and after surgery would have made the case report more demonstrative. Inclusion of only 82 out of 210 patients is also of interest.

In general, the authors undoubtedly analyzed the little-studied and interesting problem. Surgical treatment of 82 patients is unique experience in the Russian Federation and will be interesting for neurosurgeons, neurotraumatologists and neurologists.

V.A. Lukyanchikov (Moscow, Russia)
An Anatomical Study on the Applicability of Direct Endoscopic Exclusion of the Ethmoid Arteries for Devascularization of the Anterior Skull Base Structures

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The anterior skull base structures are the site of initial growth of histologically different tumors. The difficulties in their removal are often associated with significant vascularization, which may limit the amount of resection due to abundant intraoperative blood loss. Midline tumors are primarily fed by the ethmoid arteries that are not accessible to embolization. The aim of this work was a comparative experimental study of various direct approaches to the ethmoid arteries.

Material and methods. The study was conducted on anatomical specimens of 12 cadaveric heads of deceased people without pathology of the anterior skull base structures, orbits, nasal cavity, and paranasal sinuses (24 sides). In all specimens, the internal and external carotid arteries were stained with silicone. During anatomical dissection, four surgical approaches for exclusion of the ethmoid arteries were studied: 1) transorbital approach to the arteries using a bicoronal incision; 2) endoscopic retro-caruncular approach; 3) endoscopic endonasal transethmoidal approach to the ethmoid artery canals; 4) endoscopic endonasal transethmoidal transorbital approach to the ethmoid arteries in the orbit. Results. We described a surgical technique for exclusion of the ethmoid arteries using the approaches and analyzed their advantages and disadvantages. We formulated an algorithm for choosing the method for direct endoscopic exclusion of the ethmoid arteries, depending on the surgical approach chosen for removal of the tumor and features of the tumor extracranial spread. Conclusion. The decision on tumor devascularization is based on assessment of tumor blood supply (CT angiography or MR angiography data). Our study demonstrated the advantages and disadvantages of various approaches to the ethmoid arteries for their exclusion in order to early devascularize anterior skull base tumors. All these approaches are less traumatic and characterized by a good cosmetic and functional outcome.

Keywords: skull base tumor, anterior cranial fossa, endoscopy, ethmoid arteries, devascularization, surgical approach.

Abbreviations:
ICA — internal carotid artery
ECA — external carotid artery
ACF — anterior cranial fossa
CT-angiography — computed tomography angiography
MRA — magnetic resonance angiography

Tumors of various histological structure often develop within anterior skull base structures. Meningiomas of anterior cranial fossa (ACF) account for about 12–20% of all meningiomas [1, 2]. Olfactory meningiomas account for about 4.5–13% of all intracranial meningiomas [3, 4]. Surgical difficulties of these tumors are often associated with their advanced blood supply that can impair quality of resection and increase intraoperative blood loss [5]. This is especially true for tumors followed by hyperostosis and abnormal large arteries. These vessels do not retract after intersection and prevent cautery hemostasis.

Anterior skull base tumors (primarily meningiomas) are supplied from the anterior and posterior ethmoidal arteries and anterior branches of the middle meningeal artery. Anterior cerebral arteries are also involved into blood supplying of large tumors [6]. Branches of external carotid artery (ECA) (maxillary artery, middle meningeal artery) are available for endovascular embolization while occlusion of ethmoidal arteries as branches of ophthalmic artery is associated with extremely high risk of vision loss [7]. Therefore, it is necessary to analyze the opportunities for their direct occlusion prior to removal of tumor. An approach through the frontal sinus [8] using incisions within the orbit [9] and endoscopic endonasal access [10—15] are known for exclusion of the ethmoidal arteries.

The purpose of this study is to compare various approaches to the ethmoidal arteries and to identify their advantages and disadvantages in experimental anatomical research.

Material and methods

The study was conducted using specimens of head of 12 human cadavers. Death was not caused by disease of anterior skull base, orbits, nasal cavity and paranasal sinuses (24 sides). Intracarotid injection of colored silicone was applied in some cases. Four surgical approaches for occlusion of ethmoidal arteries were studied:
1) endoscopic endonasal tranethmoidal approach to ethmoidal arteries (Fig. 1a);
2) endoscopic endonasal tranethmoidal-transorbit- 
al approach to the ethmoidal arteries in the orbit;
3) retrocaruncular approach to the ethmoidal arter- 
ies (Fig. 1b and Fig. 3);
4) transorbital approach to the ethmoidal arteries us- 
ing double coronal incision (Fig. 1c).

Endoscopic dissection was carried out using 4 mm 
rigid endoscopes angled 0°, Image1 Full HD endoscopic 
camera, LED light source, specialized tools for endo-
scopic endonasal, paranasal and skull base surgery, 
AIDA DVD-M photo and video capture device (Karl 
Storz GmbH & Co. KG, Tuttlingen, Germany).

Results

Soft tissues were detached anteriorly to expose fron-
to-nasal suture and supraorbital edges of the frontal bone 
if double coronal incision was applied. Then, we dissec-
ed orbital periosteum from the upper and medial walls 
using an elevator in order to create dissection plane. After 
this, we displaced orbital content using a retractor and 
identified fronto-ethmoidal suture, sequential anterior 
and posterior ethmoidal orifices. Ethmoidal arteries were 
intersected near these orifices (Fig. 2).

Direct anterior approach to the medial wall of the or-
bit was performed in standard fashion (retrocaruncular 
access). Soft tissues were incised posterior to caruncula 
lacrimalis (Fig. 3a) towards medial wall of the orbit. Lac-
rimal structures, Horner’s muscle and other important 
structures were located anteriorly outside the approach 
trajectory (Fig. 3b). Further dissection was continued in 
subperiosteal plane between medial wall and periosteum 
of the orbit. Exclusion of ethmoidal arteries was carried 
out in similar fashion.

In case of endoscopic endonasal approach, exposure 
of anterior and posterior ethmoidal arteries required 
complete ethmoidectomy. Resection of uncinated pro-
cess, anterior and posterior ethmoidal cells was per-
formed in order to expose lamina papyracea and eth-
moidal labyrinth roof. Dissection and intersection of 
 anterior ethmoidal artery was technically simpler if it was 
located outside the ethmoidal labyrinth roof (Fig. 4a).

The first option of ethmoidal arteries occlusion sug-
gested their dissection in ethmoidal labyrinth roof. The 
second mode implied resection of medial orbital wall and 
dissection of anterior and posterior ethmoidal neurovas-
cular bundles. Ethmoidal arteries were occluded within 
the orifices of the same name (Fig. 5).

Discussion

Anterior skull base tumors especially meningioma 
are supplied from meningeal afferents within their at-
tachment to dura mater and from cortical arteries supply-
ing cortical layer of tumor. Meningeal vessels of internal 
carotid artery (ICA) pool include ethmoidal arteries as a 
rule. ECA is the main source of blood supply while affer-
ent branches of tumor may be vessels of middle menin-
geal and maxillary arteries. Meningiomas of ACF are of-
ten supplied by both ICA and ECA. Meningiomas of ol-
factory fossa and sphenoid area receive a bilateral blood 
supply from anterior and posterior ethmoidal arter-
ies [16—18].

These tumors are often highly vascularized. In this 
regard, surgical removal is associated with severe blood 
loss [5]. Preoperative embolization of supplying vessels is 
an effective technique to reduce intraoperative blood loss 
and perioperative transfusion [17, 19, 20]. As a rule, em-
bolization of the afferents is possible only from the ECA 
pool in patients with anterior skull base tumors. Selective 
embolization of ECA is performed if superselective em-
bolization of afferents from individual branches of ECA 
is impossible or in case of mixed blood supplying from 
both ICA and ECA. It is necessary for at least partial de-
vascularization of tumor and safer surgical approach. Superselective embolization of afferents (including combination with selective occlusion) is performed in other cases [21]. However, some authors [22] reported only complete embolization of supplying vessels as an effective procedure.

In general, embolization of anterior and posterior ethmoidal arteries is associated with a high risk of complications for the following reasons. First, afferents of ethmoidal arteries are usually hypertrophied and have a higher blood flow velocity [9]. Secondly, there is a certain risk of emboli migration to the cerebral arteries through the anastomoses between ICA and ECA. Embolization of anterior ethmoidal artery may be followed by retrograde dislocation of microemboli and embolism of ophthalmic artery, central retinal artery and cilioretinal arteries [23—26].

**Anatomical features of the ethmoidal arteries**

Anterior and posterior ethmoidal arteries branch from the ophthalmic artery in the orbit and accompanies nerves of the same name between superior oblique and internal rectus muscles. Arteries enter the ethmoidal labyrinth through anterior and posterior ethmoidal orifices. There are two variants of anterior ethmoidal artery passage through ethmoidal labyrinth. Course outside the ethmoidal labyrinth roof is found in 43% of cases on the right and in 49% on the left. Passage through skull base is observed in 57% of cases on the right and in 51% on the left (Fig. 4a, b) [27]. Posterior ethmoidal artery reaches the lateral edge of the cribriform plate and passes within osseous canal. Therefore, the artery is located behind the cribriform plate and anterior to the optic nerve before entering the cranial cavity (Fig. 4c).
Anterior and posterior ethmoidal orifices in the medial wall of the orbit are also characterized by variable topography. Additional orifices may be observed although only anterior and posterior ethmoidal holes are detected as a rule. Fronto-ethmoidal suture is an important anatomical landmark to reveal ethmoidal orifices (Fig. 6).

Anterior ethmoidal foramen is located within the suture in 77.7% of cases, outside the suture — in 23.3% (mean distance 0.5±2.1 mm); posterior orifice within the suture is noted in 77.25% of cases, outside the suture — in 4.25%. Additional holes are found in 25.5% of cases and always place outside the suture [28]. Anterior lacrimal crest is a permanent anatomical landmark in transorbital approach to ethmoidal arteries. The distance between anterior lacrimal crest and anterior ethmoidal foramen is 27.6±2.8 mm (range 21.6—25.1), crest and posterior ethmoidal foramen — 36.6±4 mm (range 24.1—46.1). Mean distance between anterior and posterior ethmoidal orifices is 10.6±3.3 mm (range 4.3—19.3). Proximity of posterior ethmoidal orifice to the optic canal should be considered. The distance between posterior ethmoidal orifice and optic canal is 7.4±2.9 mm (range 2.4—17.6). Finally, mean distance between anterior lacrimal crest and optic canal is 41.4±3.8 mm (range 32.9—60.8) [29].

There are two main areas for approach to the ethmoidal arteries: medial orbital wall and ethmoidal labyrinth roof [30].

Medial microsurgical approaches include transfacial (Lynch approach), pre-/trans-/ retrocaruncular approach and subperiorbital dissection in frontoorbital approach. Endoscopic approaches to medial orbital wall include endoscopic modification of Lynch approach, endoscopic precaruncular approach and transnasal-
transethmoidal approach. Approaches to ethmoidal labyrinth roof include subfrontal extradural and intradural accesses.

R. Lynch [31] described approach to the medial orbital wall in 1921. In 1946, G. Weddell et al. [32] reported occlusion of anterior ethmoidal artery through this approach. A vertical 3 cm incision is performed between the inner angle of palpebral fissure and the nasal ridge. Accurate dissection is necessary considering angular artery and vein. As soon as fronto-ethmoidal suture is exposed, it is necessary to continue dissection backwards to anterior ethmoidal foramen. This approach is associated with cosmetic disadvantages and significant risk of complications [31, 33]. Trans- and precaruncular approach is characterized by incision within the outer third of caruncula lacrimalis or immediately anterior to it. Subconjunctival dissection is further performed. Avascular fibrous tissue represented by medial palpebral ligament, orbital septum, Horner's muscle and Tenon's capsule is visualized during this approach. Fronto-ethmoidal suture is visible in approach through avascular tissue lateral to Horner's muscle and medial to orbital septum. As in the previous approach, it is necessary to continue subperiosteal dissection posterior to anterior ethmoidal foramen. Careful traction of the eyeball outwards and a deeper posterior dissection allow visualizing posterior ethmoidal foramen. The last one is located 10.6±3.3 mm (range 4.3–19.3 mm) posterior to anterior ethmoidal foramen [9, 34, 35]. Double coronal incision may be useful to skeletonize lateral and medial orbital walls downwards for sufficient traction of aponeurotic flap and visualization of the anterior ethmoidal orifice in the medial orbital wall. However, an approach to the posterior ethmoidal artery without endoscopic assistance is difficult [36].

Endoscopy-assisted approaches include modification of external transfacial access by Lynch. S. Douglas and D. Gupta described this approach in 2003. A smaller

![Fig. 5. Endoscopic endonasal approach to the ethmoidal arteries (endoscope 0°, left side). Anterior and posterior ethmoidotomies, frontotomy, sphenoidotomy are performed.](image-url)
incision (1 cm) is made between inner angle of the eye and nasal ridge up to periosteum. Next, endoscope 0° is used to find ethmoidal orifices along fronto-ethmoidal orifices and for following cautery [37]. Precaruncular endoscopy-assisted approach is also possible. A 7 mm incision is performed between the caruncula lacrimalis and the skin. Tear ducts should be catheterized to prevent strictures and violation of lacrimal fluid outflow. Intersection of soft tissue up to periosteum is followed by dissection of Horner’s muscle. Similar to the previous approach, anterior and posterior ethmoidal arteries are visualized and coagulated using 0° endoscope [38].

In 2000, T. Woolford and N. Jones [39] first described occlusion of the anterior ethmoidal artery through endoscopic endonasal approach. The authors emphasized possible intracranial and orbital complications.

There are anatomical trials devoted to occlusion of the ethmoidal arteries through endonasal endoscopic approach. The authors emphasized possible intracranial and orbital complications.

Analysis of the results of the experimental study

A comparative study of four minimally invasive endoscopic approaches to the ethmoidal arteries for their occlusion and devascularization of anterior skull base tumors revealed their advantages and disadvantages. The last ones are summarized in Table 2.

Occlusion of the ethmoidal arteries prior transcranial surgery with double coronal incision is the most successful method of early devascularization. This approach does not require additional incisions while time of surgery is only slightly increased. Dissection of supraorbital neurovascular bundles and superior oblique muscle block is a very relative disadvantage because these manipulations are inevitable during transbasal or transfrontal approach too.
### Table 1. Comparative characteristics of conventional approaches to anterior skull base tumors with dissection of the ethmoidal arteries

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfacial (by Lynch) [30, 31, 33, 42, 43]</td>
<td>No brain traction</td>
<td>Cosmetic defect</td>
</tr>
<tr>
<td></td>
<td>Convenient trajectory</td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td></td>
<td>Fast approach</td>
<td>Risk of orbital bones injury</td>
</tr>
<tr>
<td></td>
<td>Convenient access to both ethmoidal</td>
<td>Ectropion</td>
</tr>
<tr>
<td></td>
<td>arteries</td>
<td>Injury of medial palpebral ligament</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injury of lacrimal ducts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injury of optic nerve</td>
</tr>
<tr>
<td>Endoscopy-assisted transfacial [37]</td>
<td>Smaller incision</td>
<td>Cosmetic defect</td>
</tr>
<tr>
<td></td>
<td>Fast approach</td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of orbital bones injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectropion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injury of medial palpebral ligament</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injury of lacrimal ducts</td>
</tr>
<tr>
<td>Uni- and bilateral frontoorbital [36, 44—46]</td>
<td>Habitual technique</td>
<td>Risk of supraorbital nerve injury</td>
</tr>
<tr>
<td></td>
<td>No additional incision</td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td></td>
<td>Easy and fast approach to the anterior</td>
<td>Difficult approach to posterior ethmoidal artery</td>
</tr>
<tr>
<td></td>
<td>ethmoidal artery</td>
<td>Difficult approach to large tumors</td>
</tr>
<tr>
<td></td>
<td>No penetration into the orbit</td>
<td></td>
</tr>
<tr>
<td>Subfrontal extradural [36, 47, 48]</td>
<td>Habitual technique</td>
<td>Brain traction</td>
</tr>
<tr>
<td></td>
<td>No additional incision</td>
<td>Only for small tumors</td>
</tr>
<tr>
<td></td>
<td>No penetration into the orbit</td>
<td>Impossibility of complete devascularization</td>
</tr>
<tr>
<td>Subfrontal intradural [36, 47, 48]</td>
<td>Habitual technique</td>
<td>Brain traction</td>
</tr>
<tr>
<td></td>
<td>No additional incision</td>
<td>Impossibility of complete devascularization</td>
</tr>
<tr>
<td></td>
<td>No penetration into the orbit</td>
<td>Partial removal of intradural tumor is necessary for approach to the artery</td>
</tr>
</tbody>
</table>

### Table 2. Comparative characteristics of minimally invasive endoscopic approaches to the ethmoidal arteries

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic transorbital using double coronal incision</td>
<td>Short surgical channel</td>
<td>Need to mobilize supraorbital neurovascular bundle and superior oblique muscle block</td>
</tr>
<tr>
<td></td>
<td>Early devascularization of tumor</td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td></td>
<td>Occlusion of all ethmoidal arteries regardless their variability</td>
<td>Risk of optic nerve injury</td>
</tr>
<tr>
<td></td>
<td>The same incision is used as for approach to the tumor.</td>
<td></td>
</tr>
<tr>
<td>Endoscopic transorbital pre-/trans-/retrocaruncular</td>
<td>Short surgical channel</td>
<td>Need for surgical skill</td>
</tr>
<tr>
<td></td>
<td>Early devascularization of tumor</td>
<td>Additional local incision and time of surgery</td>
</tr>
<tr>
<td></td>
<td>Occlusion of all ethmoidal arteries regardless their variability</td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td></td>
<td>No need for wound closure, favorable cosmetic effect</td>
<td>Risk of optic nerve injury</td>
</tr>
<tr>
<td>Endoscopic endonasal tranethmoidal</td>
<td>Wide exposure of ethmoidal arteries in the canals</td>
<td>Need for ethmoidectomy, reaming arterial channels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long surgical channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of ethmoidal artery injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of orbital hematoma</td>
</tr>
<tr>
<td>Endoscopic endonasal tranethmoidal-transorbital</td>
<td>Wide exposure of ethmoidal arteries in the canals and from the side of the orbit</td>
<td>Need for ethmoidectomy, reaming arterial channels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long surgical channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of ethmoidal artery injury (less probable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of orbital hematoma (less probable)</td>
</tr>
</tbody>
</table>
Endoscopic endonasal approach to the ethmoidal arteries provides satisfactory visualization but it is very traumatic due to complete resection of ethmoidal labyrinth. Therefore, this technique is advisable in case of scheduled transnasal removal of tumor. However, this method is undesirable for early devascularization of tumors involving nasal cavity and paranasal sinuses because visualization of the ethmoidal arteries requires resection of tumor. Moreover, identification of the arteries may be complicated by violation of anatomical landmarks. Resection of medial orbital wall increases the efficiency of manipulation, but only if tumor’s topography does not impede this approach.

Finally, occlusion of the ethmoidal arteries in the orbit through retrocaruncular approach may be a universal and, possibly, optimal technique for early devascularization of tumor regardless the following surgical access (transcranial/transnasal). The main limitation is the need for advanced surgical experience in these procedures.

An algorithm for selecting the method of direct endoscopic occlusion of the ethmoidal arteries depending on the following surgical approach and features of extracranial lesion is proposed (Fig. 7).

Unfortunately, none of these approaches provides devascularization of tumors involving medial orbital wall since lost dissection plane between osseous wall and orbital periosteum excludes surgeon’s orientation in this anatomical area. Further anatomical studies are required to resolve the problem of occlusion of the ethmoidal arteries inside the orbit.

**Conclusion**

Decision making regarding the need for tumor devascularization should consider the grade of blood supply (CT- or MR-angiography data). Our trial has demonstrated advantages and disadvantages of various approaches to the ethmoidal arteries and their occlusion for early devascularization of anterior skull base tumors. All techniques are not traumatic and have a good cosmetic and functional outcome. The choice of certain method is determined primarily by surgical approach to the tumor. Transorbital approach to the ethmoidal arteries with a local incision may be universal although advanced surgical experience is required.

**Authors declare no conflict of interest.**
The problem of reducing blood loss in surgery for anterior skull base tumors is relevant since only few publications are devoted to this issue. In my opinion, it would be advisable to give angiographic data illustrating large afferent arteries associated with blood supply from ethmoidal arteries. It would be also desirable to discuss circulation in the ophthalmic artery. The leading role of anastomoses between middle and anterior meningeal arteries in blood supply of the orbit is possible. So, occlusion of the ethmoidal arteries may be followed by serious complications including acute retinal ischemia and subsequent loss of vision. Moreover, analysis of dynamic features of blood flow in ophthalmic artery is a difficult clinical task and requires additional trials.

The authors studied various surgical approaches for devascularization of anterior skull base tumors in the most typical clinical situations and showed their advantages and possible disadvantages. Particular attention should be paid on the proximity of the channels of posterior ethmoidal artery and optic nerve. Therefore, clipping of posterior ethmoidal artery without coagulation may be advisable due to the risk of thermal injury of the optic nerve. Another serious complication is associated with possible retraction of the arteries deep in the orbit that can lead to retrobulbar hematoma and threat of loss of vision. However, lateral canthotomy and cantholysis are effective in these cases.

G.A. Polev (Moscow, Russia)
A Comparative Study of the Efficacy and Safety of the Eyebrow Supraorbital Approach in Cerebral Aneurysm Surgery

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1Kazan State Medical University, Kazan, Russia; 2Interregional Clinical Diagnostic Center, Kazan, Russia; 3Burdenko Neurosurgical Institute, Moscow, Russia

Objective — the study objective was to compare the efficacy and safety of supraorbital eyebrow (SEA) and pterional (PA) approaches in surgery of anterior circle of Willis (ACW) aneurysms and to determine the advantages and disadvantages of SEA in aneurysm clipping.

Material and methods. The analysis included 166 patients with ACW aneurysms aged 18 to 70 years who were treated in the Neurosurgery Department of the Interregional Clinical Diagnostic Center (Kazan) in the period from 2013 to 2016. At the first stage of the study, factors affecting surgical outcomes were compared by using the Glasgow outcome scale (GOS) in subpopulations of patients operated on using SEA (n=49) and PA (n=117). At the second stage, we compared the efficacy and safety of approaches using a case-control subanalysis in appropriate subgroups of the SEA (n=37) and PA (n=37) groups. The subgroups were comparable in the following factors: gender, age, severity of subarachnoid hemorrhage (SAH) on (Fisher scale), severity of the patient’s condition (Hunt—Hess scale), size and location of the aneurysm, surgery duration, intraoperative aneurysm rupture (IOAR), amount of blood loss, rate of frontal sinus surgery, rate of nasal CSF leak, rate of intraoperative and postoperative complications, hemorrhagic and ischemic complications according to postoperative CT, patient’s satisfaction with the cosmetic result of surgery (visual analogue scale — VAS), and treatment outcomes (GOS). Treatment outcomes (GOS) and patient’s satisfaction with the cosmetic result of surgery (VAS) were considered as the efficacy parameters. The safety parameters included the amount of blood loss, rate of frontal sinus surgery, rate of nasal CSF leak, and rate of intraoperative and postoperative (hemorrhagic and ischemic) complications.

Results. At the first stage of the study, we found that the amount of intraoperative blood loss in the subpopulation of patients with ACW aneurysms who were operated on using SEA was statistically significantly less than that in the PA group (p=0.0000002). In the postoperative period, patients who underwent surgery using SEA less frequently experienced neurological deficit (p=0.003), which less frequently developed first epileptic seizures (p=0.035), and had a lower rate of hemorrhagic complications (p=0.003) and better treatment outcomes (GOS) (p=0.01). Comparison of appropriate subgroups in the SEA and PA groups, which were selected according to the control methodology and were comparable in the main factors affecting treatment outcomes, confirmed statistically significantly lower blood loss for SEA (p=0.0000002) than for PA. Compared to the SEA group, the PA group was characterized by more frequent, but not statistically significantly different, IOAR (p=1), postoperative worsening of neurological deficit (p=0.113), newly developed epileptic seizures (p=0.493), and hemorrhagic complications (p=0.0557). There were no deaths in both groups. In the SEA group, the treatment outcome was scored 4 and 5 (GOS, favorable outcome); in the PA group, the treatment outcome was scored 3 (GOS) in 2 (5.4%) patients and 4 or 5 in 35 (94.6%) patients (p=0.061). The mean subjective score of satisfaction with the treatment result (VAS) in the SEA group was significantly higher (9.4±1) than in the PA group (8.8±1; p=0.01).

Conclusion. SEA is an adequate approach for clipping ACW aneurysms, in particular ACA-AComA and MCA aneurysms, which is as effective and safe as the pterional approach.

Keywords: supraorbital eyebrow approach, pterional approach, cerebral aneurysm, case—control study.

Pt erional approach (PA) is commonly considered to be highly effective and safe in surgery for anterior aneurysms of the circle of Willis [1—4]. Reports devoted to supraorbital trans—eyebrow “keyhole”-approach (STA) occurred at the end of the 20th and the beginning of the 21st century. Many neurosurgeons described successful application of this technique in clipping aneurysms [5—23]. However, an appropriateness of this approach is still unclear [24, 25]. Some authors consider that STA is associated with advanced risk for patient and difficulties for surgeon. First of all, this position is caused by insufficient number of trials with a high level of evidence (class I and II) confirming the effectiveness and safety of STA. It is important to conduct such study in order to objectively confirm advantages and disadvantages of STA in comparison with the best conventional approach (pterional).

The majority of publications are devoted to personal surgical experience in using STA for a particular disease. This type of researches (case series) has the weakest class of evidence (class III). Conclusion about advantages and disadvantages is usually based on subjective opinion of the author in these cases, comparison of groups and randomization are not used, and results of treatment and conclusions are often questioned and challenged. There are no trials comparing STA and PA with a higher degree of evidence (class II (case control/cohort study) and class I (prospective randomized trial)). In 2013, only N. Cha-louhi et al. [26] compared STA and PA for ruptured aneurysms. The authors reported higher incidence of complications after STA and similar outcomes compared with PA. However, randomization was absent in this retrospective study.

PA has been routinely applied for anterior aneurysms of the circle of Willis since opening of the neurosurgical...
The following data were routinely recorded in the medical information system: patient’s age and gender, Hunt-Hess and Fisher grade of SAH, dimension and localization of the aneurysm, time of surgery, blood loss, incidence of the opening of frontal sinuses and postoperative nasal liquorrhea, intraoperative and postoperative complications, hemorrhagic and ischemic complications, GOS and VAS grades. Patients were examined or interviewed in 3 months after surgery.

Analysis included two stages. At the first stage, subpopulation of patients undergoing STA (STA group) was compared with those undergoing PA (PA group). The second stage consisted of case-control analysis of both subgroups. This analysis implies comparison of each patient in STA group (“case”) with certain patient in PA group with similar characteristics: age, sex, localization and dimension of the aneurysm, Hunt-Hess grade at admission, Fisher grade of SAH using the blind method (regardless results of treatment). Thus, potential influence of preoperative factors on the outcomes was assessed in both groups. The most correct evidence-based comparison of the effectiveness and safety of STA was expected.

Statistical analysis was performed in R software environment (www.r-project.org). Fisher’s exact test and \( \chi^2 \) test were used to compare variables. Wilcoxon — Mann — Whitney test was applied to analyze differences in the distributions of a continuous random variable in both groups. Differences were significant at \( p \)-value<0.05.

**Results**

The first stage of the comparative analysis of the effectiveness and safety of STA and PA in surgery for anterior cerebral aneurysms

There were 166 patients (75 men and 91 women) aged 31—69 years (mean 51.2±10.2 years). STA and PA groups were similar by age and sex (\( p=0.702 \) and \( p=0.9 \), respectively). Preoperative rupture of the aneurysm was observed in 96 (57.8%) out of 166 patients, 70 (42.2%) patients had unruptured aneurysms. PA group was characterized by significantly higher number of ruptured aneurysms in comparison with STA group (\( p=0.02 \). This feature confirms more common use of STA in less ill patients (Table 1). Dimensions and localizations of the aneurysms were also similar in both groups (\( p=0.25 \) and \( p=0.3 \), respectively). Both groups were characterized by similar number of ruptured and unruptured aneurysms depending in localization (\( p=0.5 \) (Table 2). The results of the first stage of the study are presented in Table 3.

Time of PA-associated surgery was greater by 10 min compared with STA on the average (\( p=0.158 \). Intraoperative aneurysm rupture (IOAR) occurred in 8 (16.3%) patients in STA group including 2 (4%) patients with acute period of SAH. There were 15 (12.8%) IOARs in PA

The study included patients with anterior aneurysms of the circle of Willis and to determine the advantages and disadvantages of supraorbital trans-eyebrow “keyhole” approach for clipping aneurysms.

This trial is a comparative analysis of the efficacy and safety of supraorbital trans-eyebrow and pterional approaches in the treatment of patients with anterior aneurysms of the circle of Willis. Outcomes by the Glasgow Outcome Scale (GOS) and patient’s satisfaction with the cosmetic result of surgery by visual-analogue scale (VAS) were analyzed. Safety variables include intraoperative blood loss, incidence of opening of the frontal sinuses, incidence of nasal liquorrhea, intraoperative and postoperative (hemorrhagic and ischemic) complications (Fig. 1).

The study included patients with anterior aneurysms of the circle of Willis who were treated in the neurosurgical department of the Interregional Clinical Diagnostic Center (Kazan) in 2013—2016.

**Inclusion criteria:**

1) age 18—70 years;
2) anterior aneurysms localized above the ophthalmic segment of the internal carotid artery up to A2 level of anterior cerebral artery and M3 segment of middle cerebral artery;
3) aneurysm dimension 3—20 mm;
4) Hunt-Hess grade less than IV;
5) subarachnoid hemorrhage Fisher grade less than III;
6) open clipping of the aneurysm using PA or STA.

A decision about open clipping or endovascular occlusion was made collectively by several neurosurgeons, neurologist and interventional neuroradiologist. All patients underwent CT-angiography or contrast-enhanced cerebral angiography. Surgical strategy was determined considering clinical picture and microanatomy of the aneurysm. The study included only those patients who underwent open clipping of aneurysms. Surgeries were performed under general endotracheal anesthesia. All interventions were performed by two neurosurgeons who have had sufficient surgical experience for cerebral aneurysms by 2013 (at least 70 operations). Doppler ultrasound of clipped aneurysm and great arteries was intraoperatively performed. Postoperative ICU-stay was 1 day. CT of the head was carried out within 24 hours after surgery. She same staff neurologist examined pre- and postoperative neurological status.

The purpose of this study is to compare the efficacy and safety of supraorbital trans-eyebrow “keyhole” and pterional approaches in surgery for anterior aneurysms of the circle of Willis and to determine the advantages and disadvantages of supraorbital trans-eyebrow “keyhole” approach for clipping aneurysms.
group \( (p=0.73) \). Localization and dimension of the aneurysm were not significantly correlated with intraoperative rupture \( (p=0.42 \text{ and } p=0.95, \text{ respectively}) \). Intraoperative blood loss was higher by 100 ml in PA group compared with STA group \( (p<0.0001) \). Dissection of the frontal sinus was observed in 9 (18\%) patients in STA group but none of them had postoperative nasal liquorhea or infectious complications. There were no cases of frontal sinus opening in PA group. Early postoperative epileptic seizures were not observed in STA group. In PA group, generalized epileptic seizures de novo \( (p=0.035) \) occurred in 11 (9.4\%) patients. Epileptic seizures were more common after clipping of aneurysms of anterior cerebral and anterior communicating arteries. Postoperative aggravation of motor neurological deficit was not observed in any patient in STA group. Early postoperative transient mental disorders developed only in 2 (4\%) patients. In PA group, neurological deficit impairment occurred in 33 (28.2\%) patients \( (p=0.003) \) and mental disorders were diagnosed in 7 (5.9\%) of them. There were no CT-data of postoperative ischemic complications in STA group. Only 1 (2\%) patient had post-craniotomy lamellar subdural hematoma that did not require surgical intervention. Postoperative meningal and intracerebral hematomas were observed in 11 (9.4\%) patients in PA group. Redo surgery was required in 3 cases \( (p=0.003) \). There were only favorable outcomes in STA group (GOS score 4—5) while in PA group favorable and unfavorable (GOS score 3) outcomes were observed in 112 (95.7\%) and 5 (4.3\%) patients, respectively \( (p=0.0006) \). Mortality was absent in both groups.

The follow-up data were available in 40 (81.6\%) patients in STA group and in 77 (65.8\%) patients in PA group. Mean follow-up was 23.4±12.3 (range 3—38 months) and 17.9±18.7 months (range 3—31 months) in STA and PA groups, respectively \( (p=0.09) \). Sensitive disturbances in supraorbital area occurred in 7 (17.5\%) patients in STA group. In PA group, persistent hypoesthesia near and above the suture in fronto-parietal area developed in 17 (22.1\%) patients \( (p=0.64) \). In STA group, postoperative eyebrow movement disorders were observed in 6 (15\%) patients. In PA group, 4 (5.2\%) patients had impaired lower jaw movements \( (p=0.3 \text{ and } 7 (9\%) \) patients — pain in the temporomandibular joint after surgery \( (p=0.09) \). Clear healing of postoperative wound and no infectious complications were observed in both groups. Adequate cosmetic result was achieved in all patients. Cosmetic outcomes were also assessed in 3 months after surgery (VAS). Higher score was noted in STA group compared with PA group \( (9.286±1 \text{ vs. } 8.662±1, p=0.01) \) (Table 3).

The second stage of the comparative analysis of the effectiveness and safety of STA and PA in surgery for anterior cerebral aneurysms using the case-control methodology

Selection of patients. Case-control analysis was applied due to significant differences in initial data and outcomes between both groups. These groups were created in strict accordance with the inclusion criteria as representative samples of general population. Thus, comparison subgroup was selected for 37 out of 49 patients in STA group in the ratio of 1: 1. There were no significant differences in sex and age in both subgroups \( (p=0.957) \). Surgery for ruptured and unruptured aneurysm was performed in 21 and 16 patients in each subgroup, respectively. Hunt-Hess grade I was noted in 8 (21.6\%) patients in each subgroup, grade II — in 6 (16.6\%) patients in STA subgroup and in 7 (18.9\%) patients in PA subgroup, grade III — in 2 (5.4\%) patients in STA subgroup and in 1 (2.7\%) patients in PA subgroup. Only 1 patient with Hunt-Hess grade III in STA subgroup was paired with a patient with Hunt-Hess grade II in PA subgroup \( (p=0.574) \) (Table 4).

Characteristics of aneurysms. In each of the subgroups, 2 (5.4\%) patients had aneurysm of ICA,
22 (59.5%) patients — lesion of anterior cerebral and anterior communicating arteries, 12 (32.4%) patients — middle cerebral artery. Multiple aneurysms were observed only in 1 (2.7%) patient (anterior cerebral and anterior communicating arteries) in both subgroups. Mean dimension of aneurysm was 6.77±2.78 and 6.21±2.72 mm in STA and PA groups, respectively (p=0.253) (Table 4).

The results of the second stage of the study are presented in Table 5.

Mean time of surgery was 145.0±32.8 (range 90—210) and 153.5±47.9 min (range 85—300) min in STA and PA groups, respectively (p=0.778). IOAR occurred in 5 (13.5%) patients in STA subgroup (4 of them with ruptured aneurysm) and in 6 (16.2%) patients in PA subgroup (5 of them with ruptured aneurysm) (p=1).

Mean blood loss was 111.8±76.7 (range 30–350) and 227.8±112.0 ml (range 100–550) ml in STA and PA subgroups, respectively. There was 2 times lower blood loss in STA subgroup (p=0.000000007) (Fig. 2).

IOAR was followed by intraoperative blood loss of 87.0±30.7 (range 80—350 ml) and 188.1±59.4 ml (range 50—500 ml) in STA and PA subgroups, respectively (p=0.0000000002). Dissection of the frontal sinus was observed in 6 (16.2%) patients in STA subgroup. There were no such cases in PA subgroup (p=0.0008). Nasal liquorrhea was not observed in any patient in both subgroups. There were no early postoperative epileptic seizures in STA subgroup. In PA subgroup, 2 (5.4%) patients had generalized epileptic seizures de novo (p=0.493).

Postoperative aggravation of the motor, sensory and speech neurological deficit was not observed in any patient in STA group. Only 2 (5.4%) patients with aneurysms of anterior cerebral and anterior communicating arteries had transient mental disorders. In PA subgroup, exacerbation of neurological deficit occurred in 3 (8.1%) patients (p=0.115). According to postoperative CT, only 1 (2.7%) patient in STA subgroup had lamellar subdural hematoma with no need for surgical treatment. In PA subgroup, hemorrhagic complications not required surgical treatment were observed in 7 (18.9%) patients (p=0.0557). GOS grades at discharge: only favorable outcomes were observed in STA subgroup (4 and 5 scores); in PA subgroup, severe disability was noted in 2 (5.4%) patients (p=0.063). Howevrer, good recovery (5 scores) was observed in all patients (n=16, 100%) with ruptured aneurysms in STA group. Thus, these outcomes differed significantly and favorably from similar patients with ruptured aneurysms in PA group (n=16). In this group, 2 (12.5%) patients had severe disability (3 scores) and 14 (87.6%) patients — favorable recovery (p=0.043). Mortality was absent in subgroups.

The follow-up data were available in 28 (75.6%) and 22 (59.4%) patients in STA and PA subgroups, respectively. Mean follow-up was 23.4±12.3 months (range 3—38 months) in STA subgroup and 17.9±18.7 months (range 6—31 months) in PA subgroup (p=0.043). Mortality was absent in subgroups.

Table 1. Characteristics of patients and aneurysms in STA and PA subgroups at the first stage of the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>STA, n=49</th>
<th>PA, n=117</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m, n (%)</td>
<td>23</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>f, n (%)</td>
<td>26</td>
<td>54</td>
<td>65</td>
</tr>
<tr>
<td>Age, years</td>
<td>50.8±10.0 (31—69)</td>
<td>51.3±10.4 (20—69)</td>
<td>0.702</td>
</tr>
<tr>
<td>Acute period of SAH, n (%)</td>
<td>7</td>
<td>14.3</td>
<td>38</td>
</tr>
<tr>
<td>Hunt—Hess I, n (%)</td>
<td>12</td>
<td>24.5</td>
<td>44</td>
</tr>
<tr>
<td>Hunt—Hess II, n (%)</td>
<td>6</td>
<td>12.3</td>
<td>22</td>
</tr>
<tr>
<td>Hunt—Hess III, n (%)</td>
<td>3</td>
<td>6.1</td>
<td>9</td>
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</table>

Table 2. Characteristics of the aneurysms in STA and PA groups

<table>
<thead>
<tr>
<th>Aneurysm dimension, mm</th>
<th>STA (n=49)</th>
<th>PA (n=117)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>7.2±3.3</td>
<td>6.7±2.9</td>
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</tr>
<tr>
<td>Range</td>
<td>4-18</td>
<td>4-16</td>
<td>0.30</td>
</tr>
<tr>
<td>Localization and rupture</td>
<td>In all, n (%)</td>
<td>Unruptured, n (%)</td>
<td>Ruptured, n (%)</td>
</tr>
<tr>
<td>ICA</td>
<td>3 (6.1)</td>
<td>0</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>ACA—ACoA</td>
<td>27 (55.1)</td>
<td>13 (26.5)</td>
<td>14 (28.5)</td>
</tr>
<tr>
<td>MCA</td>
<td>15 (30.6)</td>
<td>12 (24.5)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>Multiple</td>
<td>4 (8.2)</td>
<td>3 (6.1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>In all</td>
<td>49 (100)</td>
<td>28 (57.1)</td>
<td>21 (42.9)</td>
</tr>
</tbody>
</table>
Discussion

The pterional approach is traditionally used for clipping of the anterior aneurysms. Effectiveness and safety of this access have been confirmed in many studies [1—4]. Neurosurgeons aspired to develop various “keyhole”-approaches in order to minimize surgical invasiveness and complication rate [27—31]. Supraorbital trans-eyebrow “keyhole” approach has been actively used since the end of the 20th century. Many authors reported successful experience in clipping of aneurysms through this approach [5—23]. A. Pernezcky and R. Reish have the

<table>
<thead>
<tr>
<th>Table 3. First-stage data of treatment of patients with anterior aneurysms in STA and PA groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Time of surgery, min</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>IOAR, n (%)</td>
</tr>
<tr>
<td>Mean blood loss, ml</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Dissection of frontal sinus, n (%)</td>
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<tr>
<td>Postoperative epileptic seizures, n (%)</td>
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<tr>
<td>Aggravation of neurological deficit after surgery, n (%)</td>
</tr>
<tr>
<td>CT-data of hemorrhagic complications, n (%)</td>
</tr>
<tr>
<td>CT-data of ischemic complications, n (%)</td>
</tr>
<tr>
<td>Infectious complications, liquorrhea, n (%)</td>
</tr>
<tr>
<td>GOS grade, n (%):</td>
</tr>
<tr>
<td>3 scores</td>
</tr>
<tr>
<td>4 scores (satisfactory outcome)</td>
</tr>
<tr>
<td>5 scores (good outcome)</td>
</tr>
<tr>
<td>Follow-up, months</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Available catamnisis data, n (%)</td>
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<tr>
<td>Sensitive disorders within the approach, n (%)</td>
</tr>
<tr>
<td>Hypesthesia</td>
</tr>
<tr>
<td>Anesthesia</td>
</tr>
<tr>
<td>Eyebrow paresis, n (%)</td>
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<tr>
<td>VAS score of patient’s satisfaction with the cosmetic result in 3 months after surgery</td>
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<table>
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<tr>
<th>Table 4. Clinical characteristics of patients and features of aneurysms in STA and PA subgroups in case—control analysis</th>
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<tbody>
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<td>Variable</td>
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<td>Sex:</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Acute period of SAH</td>
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<tr>
<td>Hunt—Hess I</td>
</tr>
<tr>
<td>Hunt—Hess II</td>
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<tr>
<td>Hunt—Hess III</td>
</tr>
<tr>
<td>Aneurysm dimension, mm</td>
</tr>
<tr>
<td>Unruptured</td>
</tr>
<tr>
<td>Ruptured</td>
</tr>
<tr>
<td>ICA</td>
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<tr>
<td>ACA—ACoA</td>
</tr>
<tr>
<td>MCA</td>
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<tr>
<td>Multiple</td>
</tr>
</tbody>
</table>

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greatest experience of supraorbital craniotomy. For the first time, these authors scientifically substantiate and describe in detail the technique of supraorbital trans-eye-brow craniotomy and actively promoted the concept of “keyhole” surgery. These authors are deservedly recognized as the founders of supraorbital “keyhole” surgery. Their report with a large sample was published in the Neurosurgery journal in 2011. Outcomes in 1000 patients with cerebrovascular aneurysms undergoing STA-surgery had been analyzed over the past 20 years [32].

In our study, supraorbital trans-eye-brow clipping of aneurysms was applied in 49 patients, pterional approach — in 117 cases. The first stage of the study included comparison of two groups with the only significant basic difference — larger number of ruptured aneurysms in PA group. This feature indirectly indicates the use of

<table>
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<th>Variable</th>
<th>STA (n=37)</th>
<th>PA (n=37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of surgery, min</td>
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<td>0.778</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>145.0±32.8</td>
<td>153.5±47.9</td>
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</tr>
<tr>
<td>Range</td>
<td>90—210</td>
<td>85—300</td>
<td></td>
</tr>
<tr>
<td>IOAR, n (%)</td>
<td>5 (13.5)</td>
<td>6 (16.2)</td>
<td>1</td>
</tr>
<tr>
<td>Mean blood loss, ml</td>
<td>111.8±76.7</td>
<td>227.8±112.0</td>
<td>0.0000</td>
</tr>
<tr>
<td>Range</td>
<td>30—350</td>
<td>100—550</td>
<td></td>
</tr>
<tr>
<td>Dissection of frontal sinus, n (%)</td>
<td>6 (16.2)</td>
<td>0</td>
<td>0.0008</td>
</tr>
<tr>
<td>Postoperative epileptic seizures, n (%)</td>
<td>0</td>
<td>2 (5.4)</td>
<td>0.493</td>
</tr>
<tr>
<td>Aggravation of neurological deficit after surgery, n (%)</td>
<td>2 (5.4)</td>
<td>3 (8.1)</td>
<td>0.115</td>
</tr>
<tr>
<td>CT-data of hemorrhagic complications, n (%)</td>
<td>1 (2.7)</td>
<td>7 (18.9)</td>
<td>0.0557</td>
</tr>
<tr>
<td>CT-data of ischemic complications, n (%)</td>
<td>0</td>
<td>3 (8.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Infectious complications, liquororrhea, n (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>GOS grade, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 scores</td>
<td>0</td>
<td>2 (5.4)</td>
<td>0.063</td>
</tr>
<tr>
<td>4 scores (satisfactory outcome)</td>
<td>1 (2.7)</td>
<td>5 (13.5)</td>
<td></td>
</tr>
<tr>
<td>5 scores (good outcome)</td>
<td>36 (97.3)</td>
<td>30 (81.1)</td>
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</tr>
<tr>
<td>Follow-up, months</td>
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<td>0.09</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>23.4±12.3</td>
<td>17.9±18.7</td>
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</tr>
<tr>
<td>Range</td>
<td>3—38</td>
<td>6—31</td>
<td></td>
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<tr>
<td>Available catamnesis data, n (%)</td>
<td>28 (75.6)</td>
<td>22 (59.5)</td>
<td></td>
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<tr>
<td>Local hypesthesia within an approach, n(%)</td>
<td>5 (17.9)</td>
<td>3 (13.6)</td>
<td>0.715</td>
</tr>
<tr>
<td>Eyebrow paresis, n (%)</td>
<td>4 (14.3)</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>VAS score of patient’s satisfaction with the cosmetic result in 3 months after surgery</td>
<td>Mean 9.4±1</td>
<td>8.8±1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Fig. 2.** Intraoperative blood loss in pterional and trans-eye-brow supraorbital approaches.
STA in patients with less severe condition. At the first stage of the study significantly higher efficacy and safety were observed in STA group regarding intraoperative blood loss \(p=0.0000002\), incidence of postoperative neurological deficit \(p=0.003\), epileptic seizures \(p=0.035\), hemorrhagic complications \(p=0.003\) and GOS score \(p=0.01\).

Paired analysis of patients with similar baseline characteristics undergoing STA and PA surgery was performed at the second stage. This methodology made it possible to control the influence of some preoperative factors on efficacy and safety of both surgical approaches. It was concluded that STA is associated with significantly less blood loss by 100 ml on the average \(p=0.0000002\). So, this approach may be considered safer (Fig. 2). Other factors including IOAR \(p=1\), neurological deficit \(p=0.115\), epileptic seizures \(p=0.493\) and hemorrhagic complications \(p=0.0557\) were more common in PA group without significant differences between subgroups. The outcomes in both subgroups of STA and PA groups were mostly favorable and similar \(p=0.063\). The only significant negative feature of STA was dissection of the frontal sinus \(p=0.0008\). However,
it was not associated with infectious complications and nasal liquorrhoea in our sample.

STA is usually followed by a good cosmetic outcome with a barely noticeable scar despite the incision on the visible part of the face (Fig. 3). Mean VAS score was significantly higher (9.4±1) in STA group compared with PA group (8.8±1) (p=0.01). Moreover, atrophy of the temporal muscle was absent in STA group, while this complication is often observed in PA group. Temporal skull defect always remains imperceptible, as it is closed by the temporal muscle. Supraorbital numbness and eyebrow paresis regress within 3 months almost in all cases. There were no significant differences in the incidence of local sensitive disorders in STA (numbness in 5 (18.5%) patients) and PA groups (numbness in 3 (18.2%) patients) (p=0.715).

Aneurysms of anterior cerebral and anterior communicating arteries are the most suitable for clipping through STA due to favorable orientation of this approach towards the complex of anterior cerebral arteries. STA is performed medial to PA and provides better exposure of anterior communicating artery, A1- and A2-segments of ipsi- and contralateral anterior cerebral arteries compared with PA (Figs. 4, 5).

ICA aneurysms with the cupola placed on the lateral wall and bifurcation of ICA are the most suitable for clipping through STA. It is almost impossible to completely visualize and adequately clip the aneurysm if its cupula is located on posterior or medial walls of ICA. Supraclinoid segment of ICA remains closed behind small wing and anterior clinoid process due to anteromedial location of STA. Thus, segment of ICA for proximal control is reduced.

MCA aneurysms with the cupula turned forward or laterally are not difficult for clipping. PA is preferred for the aneurysms with cupula turned back and wide neck, long M1-segment of MCA. It is possible to open the sylvian fissure and enlarge the viewing angle from the lateral side in this case. Therefore, comprehensive preoperative assessment of the angiograms is essential to determine the optimal approach.

We recommend wide opening of arachnoid cisterns of the optic nerve, optic chiasm, internal carotid artery, opening of sylvian fissure and careful dissection of arachnoid adhesions during clipping of anterior aneurysms. These measures are useful to improve visibility and quality of manipulations. Long and thin instruments with a tube rod are also desirable.

Some authors reported similar viewing angle in STA and PA. However, there is no doubt that smaller craniotomy is followed by reduced space for manipulations [33—39]. Surgeon works in the same direction and plane in contrast to wider approaches with manipulations in different planes. Therefore, narrow approaches may be uncomfortable for manipulations especially in case of IOAR. It should be kept in mind that insertion of the second aspirator in the operative field may be difficult in case of aneurysm rupture. Therefore, we recommend this approach only for experienced surgeons who have repeatedly faced with IOAR. For those surgeons who want to use STA in their practice, we recommend to perform this approach on cadaveric material first. The next stage is reducing of craniotomy dimension during conventional approaches. Enlargement of the approach is always possible in these cases if STA is inadequate.

Our study demonstrates similar efficacy and safety of STA and PA. Moreover, incidence of some complications was slightly decreased in STA group despite the absence of statistical significance. Therefore, further researches with larger samples are required.

**Conclusion**

STA for anterior aneurysm clipping especially ACA-ACoA and MCA aneurysms is characterized by similar efficacy and safety as pterional approach.

**Authors declare no conflict of interest.**
It is necessary to define the term “invasion” before discussion of minimally invasive surgeries in patients with cerebrovascular aneurysms. The term “invasion” has a Latin origin and means attack, penetration and, accordingly, damage to something. Therefore, “minimally invasive surgical intervention” means surgical intervention with a minimal trauma. The first neurosurgical stage in a patient with cerebral artery disease is an approach, i.e. craniotomy. Therefore, minimally invasive surgery implies minimal trauma of not only brain matter incision. Is it possible through the ultra-small craniotomy? It is very doubtful. Moreover, the use of all modern neuroimaging complexes does not guarantee prevention of this dangerous complication. The most effective measure is accurate dissection of aneurysm-responsible artery for urgent temporary clipping in case of aneurysm rupture followed by severe bleeding. Compliance with all known precautions does not prevent the issue of ultra-small craniotomy lost the followers and eventually was caused to forget. Microsurgical repair of cerebral aneurysms is a high-risk neurosurgery. These procedures are associated with the risk of aneurysm rupture and severe bleeding. Compliance with all known precautions does not guarantee prevention of this dangerous complication. The most effective measure is accurate dissection of aneurysm-responsible artery for urgent temporary clipping in case of aneurysm rupture followed by severe bleeding. Compliance with all known precautions does not guarantee prevention of this dangerous complication. The most effective measure is accurate dissection of aneurysm-responsible artery for urgent temporary clipping in case of aneurysm rupture followed by severe bleeding.
these operations at a high level and with good results. If aneurysm clipping through ultra-small pterional or trans-eyebrow and transpalpebral craniotomy would have absolute advantages, at least tens of these hundreds of neurosurgeons would use them widely.

As above-mentioned, history of aneurysm clipping through ultra-small craniotomy is quite old. Of course, simple anterior aneurysms can be clipped through ultra-small craniotomy within sylvian fissure or supraorbital area. It is doubtful that simple anatomy of these aneurysms can be definitely confirmed prior to surgery in all cases. Moreover, advisability of these procedures in patients with acute SAH is very doubtful due to advanced risk of postoperative aneurysm rupture.

The nature around us develops according to the evolution laws. Essential part of evolution is a progress. This is true for both science and surgery. It is impossible to deceive the process of evolution. Everything that has an objective advantage finds the followers and develops. Why do we emphasize an “objective advantage”? Researchers and scientists including surgeons who are passionate about their work and super-ideas can sincerely be mistaken about something, break away from reality and lose their ability to critically evaluate the results or try to prove that they can something. For example, they prove advisability of aneurysm clipping through ultra-small craniotomy. However, there is an elementary rationalism followed by the question: is it necessary to do this?

Sh. Sh. Eliava (Moscow, Russia)
Anatomical Rationale for Surgical Treatment of Trigeminal Neuralgia Combined with Cerebellopontine Angle Tumors

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Trigeminal neuralgia (TN) can be combined with tumors of the cerebellopontine angle (CPA). The optimal surgical management in these cases depends on the anatomical relationship of the trigeminal nerve root (TNR) with tumors and vessels. The purpose of this study is to evaluate variants of the anatomical relationship between the TNR and the surrounding structures as well as to analyze the results of using various surgical techniques for treatment of TN in CPA tumors.

Material and methods. We performed a retrospective analysis of 51 patients (38 females and 13 males aged 22 to 77 years) with TN and ipsilateral CPA tumors. Space-occupying lesions were represented by 29 meningiomas of the petrous apex, 11 epidermoids, 9 vestibular schwannomas, 1 hemangioma, and 1 cavernoma.

Results. Intraoperatively, we identified 6 types of the anatomical relationships among the TNR, tumors, and CPA vessels: type I — the TNR is completely surrounded by the tumor (4 epidermoids); type II — the tumor compresses and displaces the TNR (21 meningiomas, 4 schwannomas, and 6 epidermoids); type III — the tumor occurs inside the TNR (1 cavernoma); type IV — the tumor together with the vessel compresses the TNR (3 meningiomas and 1 epidermoid); type V — the tumor displaces the TNR towards the vessel (5 meningiomas and 5 schwannomas); type VI — the tumor does not contact the TNR that is compressed by the vessel (1 hemangiomma). Preoperative MRI and intraoperative findings revealed compression and deformity of the brain stem at the TNR entry level in all but two patients. Vascular compression of the TNR (usually by the superior cerebellar artery) was found in 15 of 51 patients. Microvascular decompression (MVD) was performed using various techniques: interposition of implants between vessels and the TNR, transposition of the compressing vessels from the TNR, or transposition of the nerve root. In all patients, except 1, pain syndrome regressed immediately after tumor removal and MVD. In 1 case, the pain syndrome did not regress after total removal of epidermoid and MVD, and TN was resolved by percutaneous radiofrequency rhizotomy. Long-term postoperative follow-up results showed complete elimination of TN in all cases; there were no persistent neurological complications and postoperative mortality.

Conclusion. TN may result from direct compression and deformation of the TNR and brain stem by CPA tumors. In some cases, the cause of TN is combined compression of the TNR by the tumor and vessels. Assessment of the neurovascular relationships requires detailed examination of the entire TNR after tumor removal. In the case of vascular compression of the TNR, various MVD techniques can be used for treatment of TN.

Keywords: trigeminal neuralgia, cerebellopontine angle, trigeminal nerve root, tumor, microvascular decompression.

Abbreviations:
SCA — superior cerebellar artery
MVD — microvascular decompression
CPA — cerebellopontine angle
MRI — magnetic resonance imaging
AICA — anterior inferior cerebellar artery
TN — trigeminal neuralgia
CN IV — trochlear nerve
CN V — trigeminal nerve root
CNs VII—VIII — facial and vestibulocochlear nerves

Intracranial tumors of various localization and morphological structure resulted different syndromes of facial pain. Clinical manifestations of typical trigeminal neuralgia (TN) significantly differ from neuropathic facial pain characterized by prolonged or persistent pain with sensitive disorders [1—4]. E. Bullit et al. [5] analyzed 16 patients with intracranial tumors and facial pain. They reported TN in 6 out of 7 patients with cerebellopontine angle tumors and only in 2 out of 9 patients with lesion of anterior cranial fossa and peripheral trigeminal nerve. A. Puca et al. [6] investigated the clinical manifestations of trigeminal nerve lesion in 73 patients with intracranial tumors and found TN and atypical TN in 12% and 2% of patients with CN V compression within CPA, respectively. The authors did not diagnose TN in patients with tumors near trigeminal ganglion and peripheral trigeminal nerve [6].

A. Revilla [7] analyzed outcomes in 473 patients with TN and identified ipsilateral CPA tumors in 24 (5.1%) cases including neuromas in 11 (46%), epidermoids in 9 (38%) and meningiomas in 4 (16%) patients. Similar data are found in later studies with larger sample sizes. Thus, incidence of CPA tumors was 9.5% among 1257 patients with TN. In the other series of 1211, 1930 and 2070 patients this value was 2.1%, 1.4% and 1.7%, respectively. Meningiomas, acoustic neuromas and epidermoids were more common [8—11].

TN is usually considered as a result of the direct effect of CPA tumor on the trigeminal nerve root. Essential role of direct compression, deformation and dislocation...
of nerve fibers is confirmed by the high incidence of paroxysmal facial pain regression after surgical removal of tumors. Analysis of topographic features of TN combined with CPA tumors found vascular compression of CN V as an additional or leading factor in the development of neuralgic syndrome. F. Barker et al. [9] emphasize that TN in patients with CPA tumors has a vascular cause and occurs due to nerve compression by an adjacent vessel. K. Hasegawa et al. [12] determined 4 topographic types of interrelationships of CN V with tumors and vessels. These types include not only effects of tumors per se, but also compression of nerve fibers with arterial vessels.

Treatment of TN implies removal of CPA tumors and vascular decompression of CN V. However, surgical strategy depends on various anatomical features which often lie beyond the four types described by K. Hasegawa et al. [12]. Topographic features of CN V and CPA tumors resulted modification of surgical technique of vascular decompression which is performed at the final stage of surgery for TN [13].

Anatomical features and relationships of CN V and adjacent structures are studied in patients with TN and CPA tumors in this study. The outcomes of surgical decompression for paroxysmal facial pain are also described.

Material and methods

The inclusion criterion for 51 patients was clinical picture of typical TN and ipsilateral CPA tumor. Patients with typical TN and contralateral CPA tumors or other intracranial neoplasms were excluded. Patients with CPA tumors followed by neuropathic facial pain and those with benign and malignant neoplasms of the middle cranial fossa associated with deafferentation or facial pain syndrome due to lesion of trigeminal nerve root, trigeminal ganglion and peripheral trigeminal nerve were also excluded.

The cause of TN was refined during CPA exploration. Resection of tumor was followed by neurovascular decompression if it was necessary. Surgical treatment was performed in 51 patients (38 women and 13 men aged 22—77 years). Right-sided CPA tumors and TN were observed in 24 cases, left-sided — in 27 cases. Preoperative duration of disease ranged from 1 month to 20 years. All patients received carbamazepine 400—2000 mg daily to reduce the intensity of pain syndrome. Seven patients underwent trigeminal nerve repair with a mild transient effect. Previous radiosurgery did not reduce TN in 3 cases. All patients underwent clinical and neurological examination including CT and MRI in preoperative and early postoperative period. Retromastoid approach in patient’s sitting position under endotracheal anesthesia was applied to analyze topographic features of CN V and adjacent structures and to remove the tumor.

Results

CPA tumors included meningiomas in 29 cases, epidermoids — in 11, neuromas — in 9, cavernoma — in 1 and hemangioma — in 1 patient. All meningiomas were growing from the dura mater of the apex of petrous part of temporal bone anterior to internal auditory meatus. Dimensions of tumors ranged from 19 to 65 mm. There was a spread of tumor up to the adjacent parts of clivus in 7 patients (petroclival tumor), involvement of cerebellar tonsil was noted in 11 patients (petroso-tentorial tumor). All neuromas were growing from the vestibular nerve (dimension range 20—50 mm). Dimensions of epidermoids ranged from 20 to 60 mm. Involvement of contralateral CPA was noted in 3 cases, filling of paracerebellar cisterns — in 2 cases. One patient had hemangioma of 11 mm localized on the dura mater above and anterior to internal auditory meatus. In another patient, 5 mm cavernoma was lying inside trigeminal nerve root.

Anatomical interrelations of CN V; CPA tumors and adjacent vessels identified during surgical exploration were divided into 6 types (Fig. 1):— type I — tumor completely surrounds TNR;— type II — tumor displaces TNR;— type III — tumor is placed inside TNR;— type IV — tumor and adjacent vessel displace TNR;— type V — tumor displaces TNR towards the vessel;— type VI — tumor is not in contact with TNR which is compressed by the vessel.

In our sample, TNR compression according to these types was distributed as follows: type I — in 4 patients, type II — in 31, type III — in 1, type IV — in 4, type V — in 10 and type VI — in 1 patient. The variants of anatomical relationships of TNR with CPA tumors of various histological structure and adjacent vessels are presented in the table.

Removal of tumor alone was performed in patients with anatomical types I, II and III. Types IV, V and VI were managed by additional vascular decompression of TNR.

CPA tumors followed by dislocation and deformation of TNR was diagnosed in 50 patients; there was no direct contact of the nerve fibers with a tumor in one case. TNR was stretched on tumor surface in 7 out of 11 patients with epidermoid. Deformed and displaced nerve root was placed inside the tumor in 4 patients (Fig. 2).

In patients with meningiomas, TNR displacement direction depended on the location of tumor matrix. TNR was located on posteroinferior surface of the tumor growing near the apex of petrous part of the temporal bone and petro-clival area. Meningiomas growing from the dura mater of petrous part of the temporal bone near internal auditory meatus and vestibulocochlear neuromas were followed by anterior and medial dislocation of TNR to the anterior surface of the tumor (Fig. 3).
Brain stem deformity within the entrance of sensory fibers of TNR was observed in 49 patients. Contact with pontine surface was only observed in cases of intraneural cavernoma and small hemangioma. The greatest dislocation of fibers was noted throughout the segment along brain stem while peripheral fibers near trigeminal notch were slightly deformed. These fibers were easily dissected from the tumor due to intact arachnoid membrane. Complete removal of cavernoma occupying a significant part of TNR was carried out by dissection along hemisiderin border to preserve intact nerve fibers (Fig. 4). All arachnoid adhesions between TNR and brainstem were intersected after removal of tumor in order to eliminate dislocation and deformation of nerve fibers.

Neovascular conflict was not identified at the beginning of surgical interventions as a rule due to tight contact of TNR and deformed brainstem and poor visualization of vessels behind the tumor. Excision of tumor was followed by assessment of topographic relationships of TNR and vessels in order to determine further surgical strategy. We did not affect cerebellar arteries displaced and fixed to brain stem by arachnoid adhesions due to no compression of TNR.

Vascular compression was easily diagnosed in apical meningiomas of petrous part of the temporal bone. Displaced downward superior cerebellar artery (SCA) and its branches intruded TNR near the brain stem. Neovascular conflict was found in 15 cases. Technique of vascular decompression depended on tension and deformation of TNR. Interposition procedure was used for a slight elongation of TNR fibers. This method consisted of deployment of implants (auto-tissue, synthetic materials) between brain stem, nerve root and vessel (Fig. 5).

We also performed transposition of compression-related vessel. This vessel was fixed to dura mater, cerebellum and brain stem after arachnoid dissection without contact of the implants with trigeminal entry zone (Fig. 6).

Another approach to vascular decompression was used only for significant stretching of TNR between tumor and artery. Vascular decompression implied nerve root mobilization. Intersection of arachnoid adhesions with brain stem led to free displacement of TNR without its contact with arterial vessel. This approach to TNR transposition did not require implant deployment to fix new topographic relationships between nervous and vascular structures (Fig. 7).

Compression of trigeminal entry zone by ponto-trigeminal vein was observed in one case after removal of hemangioma that was not in contact with TNR. This vein was coagulated and excised to eliminate neovascular conflict.

Postoperative MRI confirmed total removal of 50 CPA tumors. Residual epidermoid in contralateral cerebellopontine cistern was found only in 1 case. There were no lethal outcomes after surgical interventions while transient postoperative paresis of cranial nerves regressed after 2—3 months. Occurrence or aggravation of sensory disorders of trigeminal nerve were diagnosed in 15 cases. These disturbances recovered within a few weeks and were not associated with recurrent TN. An improvement of facial sensitivity was noted in 6 patients without previous surgical interventions on TNR and its peripheral branches.

Complete regression of TN in early postoperative period was observed in 50 patients. One patient with paroxysmal pain for a one week after removal of epidermoid required percutaneous radiofrequency trigeminal rhizotomy. There were no recurrent CPA tumors and TN within 2—10 years postoperatively.

Discussion

Patients undergoing TNR exploration for treatment of TN have CPA tumors in 0.9—9.9% of cases while incidence of TN associated with various morphological types of ipsilateral tumors is different [6—11, 13—19]. Our sample included patients with hemangioma and cavernoma besides those with meningiomas, neuromas and epidermoids. This is due to the fact that hemangiomas and cavernomas manifest themselves as volume formations in this case, and their proliferative potential is very diverse [35]. W. Dandy [15] reported TN in 16.7% of cases among 186 patients with CPA tumors. Vestibular schwannomas were associated with TN in 10% (16/160) of cases, meningiomas — in 38.5% (5/13), epidermoids — in 76.9% (10/13) of cases. A. Puca et al. [6] found TN in 9 out of 73 patients with CPA tumors. Vestibular schwannomas were accompanied by TN in 3.3% of cases (in case of large tumors as a rule). TN is one of the leading symptoms in CPA epidermoids and found in 29.7% of patients. It is the second common symptom after hearing impairment (37.6% of cases) [17, 20—23].

F. Barker et al. [9] collected 232 cases of TN combined with CPA tumors in previously published reports and found meningiomas, neuromas and epidermoids in 40, 22 and 38% of patients, respectively. H. Kobata et al. [17] analyzed 515 patients with TN and diagnosed CPA tumors in 51 (9.9%) cases including meningiomas in 16 patients, neuromas — in 7, epidermoids — in 28 patients.

TN is rarely observed in patients with CPA tumors. In most cases, meningiomas and neuromas are associated with sensory impairments and neuropathic facial pain. B. Neff et al. [2] analyzed trigeminal nerve dysfunction in 50 patients undergoing surgery for large vestibular schwannomas adherent to TNR. They found impaired facial sensitivity in 88% of cases, paresthesia in 24%, pain syndrome including TN and neuropathic facial pain — in 20% of patients. S. Ichimura et al. [24] studied 91 patients with petro-clival meningiomas. The authors noted that radiculopathic symptoms including hypesthesia or TN were common in patients with apical tumors petrous part of the temporal bone. Currently, pathogenesis of TN in
Fig. 1. Types of anatomical relationships of CPA tumors with trigeminal nerve root and vascular structures (arterial vessels are highlighted in red).
Table: Relationships of TNR with CPA tumors and vessels

<table>
<thead>
<tr>
<th>Type</th>
<th>meningioma (29)</th>
<th>neuroma (9)</th>
<th>epidermoid (11)</th>
<th>hemangioma (1)</th>
<th>cavernoma (1)</th>
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<td>Vascular compression</td>
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<td>SCA*</td>
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<tr>
<td>SCA + AICA**</td>
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<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>PTV***</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
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</tbody>
</table>

Footnote: *SCA — superior cerebellar artery; **AICA — anterior inferior cerebellar artery; ***PTV — ponto-trigeminal vein.

Fig. 2. CPA epidermoid (type I).

a — preoperative MRI, deformed TNR is located inside the tumor; b — TNR is inside the epidermoid filling cerebellopontine cistern; c — loops of superior cerebellar artery are on the surface of the pons; d — deformed TNR and cranial nerves VII—VIII (facial and vestibulocochlear) with AICA are visualized after removal of tumor.
patients with CPA tumors is still unclear. However, W. Dandy [15] reported relatively common TN in small tumors contacting with nerve root and rarity of paroxysmal facial pain in patients with large tumors followed by severe nerve fiber deformation. Deformation and compression of TNR by a slowly growing tumor may be accompanied by TN. In our sample, paroxysmal facial pain was predominantly caused by direct tumor effect, although direction of TNR displacement and its relationships with the tumor were not essential for the development of TN.

Additional compression of TNR by arterial vessels in patients with brain stem tumors is described in case reports and several publications summarizing a significant number of patients with TN undergoing surgical exploration of CPA [8–13, 17, 19, 25–28]. F. Barker et al. [9] found 21 patients with additional compression of TNR by arterial and venous vessels among 26 patients with TN and CPA tumors (14 meningiomas, 8 vestibular schwannomas, 2 epidermoids, 1 ependymoma and 1 angiolipoma). M. Liu et al. [10] reported neurovascular conflict in 17 out of 27 patients. The conflict was mainly caused by
SCA and diagnosed in patients with meningioma (8/11), epidermoid (7/13) and neuroma (2/3). P. Liu et al. [11] found SCA-associated vascular compression of TNR in 15 out of 35 patients with TN and CPA tumors. Compression accompanied meningiomas in 10 out of 16 cases, epidermoids — in 3 out of 14 cases, acoustic schwannomas — in 2 of 4 cases. Y. Wei et al. [27] also analyzed 39 patients with TN and CPA tumors. Epidermoid was diagnosed in 23 patients, acoustic schwannoma— in 9 patients, meningioma — in 6 patients, lipoma — in 1 patient. Compression of TNR by tumor and vessel was intraoperatively diagnosed in 23 patients. CPA epidermoid relatively often manifests by TN and is also associated with vascular compression of TNR. H. Kobata et al. [17] observed this complication in every third patient.

Vascular compression of TNR in patients with TN combined with ipsilateral CPA tumors is represented by anatomical types IV, V, and VI. Tumor-associated displacement of the vessels into trigeminal entry zone (type IV) results unilateral compression of TNR by the tumor and the vessel. Tumor-associated TNR displacement towards “normally” located vessel (type V) results bilateral compression of the nerve root between tumor and artery or vein adjacent to the root on the opposite side.

Vascular compression of TNR is leading aspect in the pathogenesis of TNin patients with small CPA tumors located away from the trigeminal entry zone (type

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**FIG. 4.** Cavernoma of trigeminal nerve root (type III).

a — preoperative MRI, tumor is inside the TNR; b, c — tumor is under pial membrane, superior cerebellar artery is not in contact with TNR; d — tumor removal is followed by resection of posteroinferior parts of TNR.
VI). M. Samii and C. Matthies [26] reported 9 patients with TN and vestibular schwannomas slightly extending from the internal auditory meatus and followed by vascular compression of trigeminal entry zone. Compression was caused by branches of SCA in 8 cases, superior petrous vein — in 1 case. J. Miller et al. [28] demonstrated high efficacy of vascular decompression for small trigeminal neuromas followed by clinical picture of TN and tumors were not subjected to surgical manipulations.

Different clinical manifestations of pain syndrome caused by lesion of proximal and distal segments of trigeminal nerve confirm the existence of anatomical factors leading to TN in patients with CPA tumors. A. Lagares et al. [29] performed biopsy of TNR in a patient with TN and CPA epidermoid and observed ultrastructural signs of central demyelination of the nerve root. Cavernoma of TNR associated with TN is also characterized by the changes similar to morphological signs of demyelination in case of vascular compression [30, 31]. We have analyzed the anatomical relationships of TNR and adjacent tumors and vessels in our sample. It was found that TN may be due to demyelination of trigeminal entry zone as a result of TNR compression by small, large tumors and vessels with occurrence of cross neurovascular conflict. In all cases, the most severe compression of TNR, caused by isolated or combined effects of tumors and ves-

Fig. 5. Apical meningioma of petrous part of the temporal bone with TNR compression by superior and anterior inferior cerebellar arteries (type IV).

a — preoperative MRI. SCA is located between the tumor and deformed brainstem; b — dislocated SCA is located in trigeminal entry zone; c — SCA is dislocated upwards along the pons, TNR is compressed by the loop of AICA; d — an implant is installed between displaced AICA and TNR.
vessels, was observed near the brain stem. The majority of patients with CPA tumors and TN had brain stem deformity that indicates compression of the entire trigeminal entry zone. Trigeminal root entry zone is represented by three components of the nerve root: 1) transition zone, 2) nerve segment adjacent to the brain stem with central myelin, 3) initial segment inside the brain stem. The length of glial segment of TNR from pontine surface to Obersteiner-Redlich’s zone varies considerably and is about 5 mm. Segment with central myelin can spread up to the middle of cisternal segment of the nerve root [32, 33]. Compression of transition zone, glial segment of TNR and segment inside the brain stem by tumors and vessels results local demyelination of axons. This lesion manifests by paroxysmal facial pain through peripheral and central pathophysiological mechanisms [3, 4, 29, 31].

Regression of TN caused by CPA tumors occur not only due to TNR decompression but also due to intraoperative mechanical and thermal effects on the nerve fibers. Mild intraoperative injury of the fibers and vessels results segmental facial sensory denervation and subsequent sensitive disorders. In these cases, denervation with fast postoperative regression of paroxysmal pain is

**Fig. 6.** Apical meningioma of petrous part of the temporal bone with TNR compression by superior cerebellar artery (type IV).

a — preoperative MRI, brain stem and trigeminal entry zone are deformed by the tumor; b — displaced and elongated TNR is compress by a loop of SCA; c — artery is dislocated from a trigeminal entry zone; d — SCA is fixed to tentorium cerebelli.
performed in the form of trigeminal rhizotomy. Clinical efficacy of this procedure is not related to TN etiology while duration of remission depends on severity and extent of numbness [3, 13, 30]. Long-term disappearance of TN in patients without postoperative sensitive disorders or with recovered previous sensory disturbances confirms an essential role of tumor and vascular decompression of TNR. Removal of CPA tumors and vascular decompression should be always completed by intersection of all adhesions between TNR and adjacent structures. This measure leads to release of nerve fibers and decrease of their deformation. The following recovery of myelin sheaths of TNR leads to permanent disappearance of TN. However, mild paroxysmal facial pain can occur within a few days and weeks after surgery due to slight intraoperative injury of trigeminal nerve. These episodes may be reduced by medication. Similar delayed efficacy is also observed in case of minimal contact with TNR during vascular decompression with isolated manipulations on arteries and veins [34].

**Conclusion**

Typical TN may be caused by CPA tumors due to compression and deformation of root entry zone and brain stem. These tumors are apical meningiomas of petrous part of the temporal bone, epidermoids and vestibular schwannomas. The main goal of surgical treatment
of TN associated with CPA tumors is removal of tumor followed by root entry zone decompression. Microsurgical removal of tumor with trigeminal root decompression should be preferred for CPA neoplasms followed by brain stem compression. Destructive procedures on the trigeminal nerve including stereotactic radiosurgery may be effective for TN caused by small tumors without significant brain stem and cranial nerve compression, in patients with somatic contraindications for surgery and in case of patient’s unwillingness to be exposed to the risks associated with surgical treatment [36].

Removal of tumors and intersection of adhesions of TNR are accompanied by complete and long-term regression of paroxysmal facial pain. Visualization of the entire cisternal segment of TNR is essential during resection of the tumor in order to diagnose possible neurovascular conflict. Arterial or venous compression of the root entry zone should be eliminated by deployment of implant between TNR and the vessel, vessel transposition or displacement of the nerve root. Identification of the anatomical relationship of tumor, TNR and vessels is necessary to determine optimal surgical strategy.

Authors declare no conflict of interest.


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**Comment**

The article is devoted to a very important issue — treatment of trigeminal neuralgia in patients with CPA tumors. Well-documented information about possible explanation of etiology, pathogenesis and appropriate approaches to surgical interventions should be emphasized. Based on long-term personal experience, the authors expanded the classification proposed almost 25 years ago to the types of anatomical relationships between tumors and trigeminal nerve root and illustrated all types with well-chosen clinical examples. The article is very well written and fits all the requirements and international standards of scientific literature.

I would like to note that the question of whether the cavernoma is a tumor remains open. The majority of reputable neurosurgical researches determine cavernoma as vascular malformation.

In the future, analysis of this issue will imply study of optimal treatment strategy in patients who contraindications for open surgery, advanced age patients or those with unwillingness to undergo surgery. Another question is influence of certain type of relationship between tumor and TNR on choice of surgical approach and feasibility of surgery per se.

*K.V. Slavin (Chicago, USA)*
Primary sacral tumors account 2–4% of all osseous neoplasms and 1–7% of all primary spinal tumors. These tumors include congenital neoplasms (chordoma, teratoma), primary bone tumors (chondrosarcoma, giant cell tumor, osteoblastoma, aneurysmal bone cyst, osteoma, chondroma), various soft tissue sarcomas. Separately, neurogenic tumors are distinguished: ectopic ependymomas, neurinomas, neurofibromas, malignancies of the peripheral nerves, peripheral neuroectodermal tumors (PNET) [1, 2]. Clinical picture of these neoplasms is different and depends on tumor dimension, direction of growth, spread and invasion grade. However, local pain getting worse at night is the first symptom as a rule [3].

Surgical treatment of sacral tumors is associated with various postoperative complications; prognosis is ambiguous and predominantly determined by the biological features of the tumor [4, 5]. The classification of symptoms after en-bloc sacrectomy proposed by Biagini et al. in 1997 is shown in Table 3.

In our sample, 10 patients with sacral tumor underwent en-bloc sacrectomy (6 patients with chordoma, 2 with giant schwannoma, 1 with ganglioneuroma, 1 with solitary metastasis of kidney cancer). All patients had severe preoperative local pain syndrome (7 scores by visual analogue scale, VAS), 6 patients (with chordoma and schwannoma) had pelvic organ dysfunction in the form of constipation and impaired urination, 2 patients had anogenital anesthesia.

All patients with chordoma (n=6) underwent sacral resection: high amputation of the sacrum -3 patients, top-
Complications of sacrectomy

Analysis of the results of sacrectomy requires clarifying the concepts of postoperative consequences and complications.

The consequences of sacrectomy are disorders associated with intersection of nerve structures during tumor dissection, violation of pelvic floor integrity and appearance of a cavity in the sacrum. Thus, consequences of surgery include impaired sensitivity within anogenital area and in legs, impaired movement of legs, impaired sexual function, urination, defecation.

Complications of sacrectomy are divided into intraoperative, early and long-term postoperative ones (Fig. 1). Postoperative complications were observed in 37 (68%) patients. Six patients had intraoperative complications. All 37 patients had complications in early postoperative period. There were no long-term complications. Overall number of complications was 47.

Intraoperative complications

Intraoperative complications include injury of great vessels, intraoperative blood loss, perforation of hollow organ wall, spontaneous intersection of spinal roots.

Only blood loss not associated with great vessel injury was observed in study patients. It was caused by damage of presacral veins and rectal venous plexus. Mean blood loss was 3.2 liters (range 1.6—17). Cell-saver reinfusion system with a leukocyte membrane, hypervolemic hemodilution with simultaneous sampling of autologous red blood cells, preoperative sampling of autologous plasma and donor red blood cells and plasma were used to prevent the consequences of blood loss. Severe blood loss and transfusion of donor red blood cells were followed by shock kidney and severe hematuria in one case. This complication was successfully cured in early postoperative period.

Early postoperative complications

Early postoperative complications include wound complications. According to the literature, these events account 25—46% of all complications. Infectious complications including superficial and deep suppuration prevail. Deep suppurations consist of ischiorectal abscess, empyema, congestive abscess and epididymitis followed by meningitis. These complications usually accompany rectal wall injury with subsequent bacterial dissemination throughout the wound and suppuration.

In our sample, supplicative complications occurred in 10 (27%) patients including 6 cases of deep suppuration. Deep suppuration required redo surgery followed by inflow-outflow drainage of the wound. Open management of the wound with an aspiration dressing was required in 1 case. Suppuration of intermuscular hematoma was observed in 1 patient (Fig. 2). Postoperative sepsis was diagnosed in 1 patient. This is a common event and usually occurs in patients with bone tumor undergoing partial sacrectomy. Any consequences are rarely observed.

In a 78-year-old patient B., high amputation of the sacrum partially involved m. erector spinae. Large glutus muscles were used to repair the defect, the left flap was partially turned. Patient had body underweight caused by severe pain syndrome. In particular, the last one accompanied defecation. In this regard, the patient tried to eat less that has led to decrease of body weight from 86 to 65 kg for 1 month. Reparative dysfunction resulted impaired healing and adhesions of soft tissues followed by occurrence of the cavity with serous fluid and overall volume of 5 liters (Fig. 3).

Transposition of the rectoabdominal flap into presacral area through rectoabdominal approach is used for these complications (Fig. 4). There were regression of serous cavity and clear healing of the wound after 10 days despite continued growth and metastases (chondroid-chordoma GIII).

Bladder dysfunction was observed in 15 patients. Only 3 patients had these disorders as a result of sacrectomy while in others pelvic organ dysfunction was associated with intraoperative injury or other effects on the sacral roots. Pelvic organ dysfunction manifested by complete

<table>
<thead>
<tr>
<th>Tumor</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital tumors</td>
<td>10</td>
<td>17.5</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Teratoma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Cartilage tumors</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Chondroma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Neurogenic tumors</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Schwannoma/neurofibroma</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone tumors</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Hemoblastosis</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Plasmocytoma</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Tumor-like diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Fibroma</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>In all</td>
<td>57</td>
<td>100</td>
</tr>
</tbody>
</table>
Urinary retention in 12 patients that required periodic catheterization in 11 cases and insertion of permanent catheter in 1 patient with impaired mobility. Complete urinary retention was complicated by acute pyelonephritis in 1 patient. Urinary incontinence developed in 3 cases including 2 patients with paradoxical ischuria and 1 patient with complete urinary incontinence. Two patients also noted no urge to defecate, impaired defecation and associated abdominal pain. Colostomy was formed in 1 patient.

Urine retention disorders in 13 patients completely regressed or resulted in incomplete retention with minimal residual urine (up to 150 ml). Intersecion of the dural sac at the level of L5—S1 resulted permanent dysfunction of the pelvic organs in 1 patient. Epicystostomy was imposed in this patient. Bladder neck wrapping was performed in 1 patient with urinary incontinence.

Early postoperative liquorhea occurred in 6 patients. All patients had advanced neurogenic tumors including mixopapillary ependymoma (n=5) and intra-extradural schwannoma (n=1). Removal of these tumors was associated with dura mater repair. Lumbar drainage was applied in all patients until complete healing of the wound. Infectious complications were absent, liquorhea did not require surgical repair.

Pain caused by intersection/injury of sacral roots may be complicated by chronic neuropathic pain syndrome resistant to medication. In our sample, chronic neuropathic pain syndrome within S2—S5 innervation

<table>
<thead>
<tr>
<th>Table 2. Major symptoms in patients with various sacral tumors at admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type/ Symptom of tumor</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Congenital tumors</td>
</tr>
<tr>
<td>chordoma</td>
</tr>
<tr>
<td>teratoma</td>
</tr>
<tr>
<td>Cartilage tumors</td>
</tr>
<tr>
<td>chondroma</td>
</tr>
<tr>
<td>Giant cell tumor</td>
</tr>
<tr>
<td>Neurogenic tumors</td>
</tr>
<tr>
<td>ependymoma</td>
</tr>
<tr>
<td>schwannoma/neurofibroma</td>
</tr>
<tr>
<td>ganglioneuroma</td>
</tr>
<tr>
<td>malignant peripheral nerve sheath tumors</td>
</tr>
<tr>
<td>Bone tumors</td>
</tr>
<tr>
<td>osteoblastoma</td>
</tr>
<tr>
<td>hemoblastosis</td>
</tr>
<tr>
<td>plasmocytoma</td>
</tr>
<tr>
<td>lymphoma</td>
</tr>
<tr>
<td>Metastatic tumors</td>
</tr>
<tr>
<td>Vascular tumors</td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Tumor-like diseases</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
</tr>
<tr>
<td>fibroma</td>
</tr>
<tr>
<td>In all, %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Classification of impairments after sacrectomy by Biagini et al. (1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function or organ with impaired function</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Motor</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bladder</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bowel</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
**Fig. 1.** Classification of complications of sacrectomy.

**Fig. 2.** MRI of the sacrum and pelvis in a patient with sacral chordoma.

- **a** — preoperative sagittal scan, the tumor is indicated by an arrow; **b–d** — postoperative sagittal (b) and axial scans (c, d). Suppuration of intermuscular hematoma is indicated by an arrow.
zone were observed in 4 patients. Complete regression of pain syndrome within 3 months was noted in 3 cases, while long-term intake of pregabalin was required in another one.

Sacral stress fracture early after high sacrectomy occurred in 4 cases. In the literature, sacral stress fracture is described as a rare complication after sacrectomy due to wide application of osteosynthesis. In our sample, the fracture was due to partial sacrectomy in patients older 40 years with concomitant osteoporosis (3 women and 1 man) (Fig. 5). This complication occurred after surgery for chordoma in 3 cases. Another case was patient with S1 root schwannoma undergoing partial sacrectomy and enlargement of the first sacral orifice (Fig. 6). This complication was accompanied by local pain syndrome and gait disturbance in all cases. Deployment of metal implants for lumbar-pelvic stabilization was performed in the first 3 cases (Fig. 7). Pain syndrome relief was observed after bisphosphonates administration in 1 case.

Technique of sacrectomy is difficult and often associated with a large number of complications. Personalized approach is essential to determine optimal surgical treatment. It is necessary to evaluate patient’s functional status and feasibility of surgery, to compare the goals of treatment, consequences and possible complications and

Fig. 3. Giant serous cavity as a complication of sacrectomy (arrow).

Fig. 4. Transposition of pedicled rectoabdominal flap.
a — sagittal MR-scan after surgery. Rectoabdominal flap is indicated by an arrow; b — scheme of flap transposition.
Fig. 5. Sacral stress fracture after high amputation of the sacrum in a 54-year-old patient.
a, b — 3D CT-scan of the pelvis after surgery, anterior (a) and posterior view (b); c — axial CT-scan at the level of fracture. The arrows indicate the fracture line.

Fig. 6. CT-scan of the pelvic bones.
a — frontal and sagittal planes; b, c — 3D-reconstruction, anterior and posterior view. The arrows indicate the fracture line.
to take into account the biological properties of a particular tumor.

Optimal strategy for wound and orthopedic complications is simultaneous transposition of the rectoabdominal flap and lumbar-pelvic stabilization.

Authors declare no conflict of interest.
REFERENCES


Received: 22.03.18

Comment

The article is written in classic style. Analysis of surgical complications included 57 patients with sacral tumors. Complications of sacral tumor surgery is a truly important and widely discussed problem in English-language literature. The problem of surgical treatment of sacral tumors is surely relevant since over third of patients have impaired quality of life and need for redo surgery after partial or total sacrectomy.

The authors analyzed heterogeneous group of patients. Only localization of tumors was similar. Of course, surgical technique depended on morphological structure of the tumor. The authors emphasize correlation of certain complications and surgical technique including extent of nervous structure resection.

The article is of interest for readers of the journal due to rarity of sacral tumors.

*A.O. Gushcha (Moscow, Russia)*
Secondary Spondylogenic Epidural Abscess

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1Regional Clinical Hospital №2, Tyumen, Russia;
2Tyumen State Medical University, Tyumen, Russia

The article presents the results of a retrospective analysis of 200 patients with hematogenous osteomyelitis of the spine who were treated in the Tyumen Regional Clinical Hospital №2. Neurological disorders were present in 37 patients (group I); 163 patients (group II) had no neurological disorders; according to CT and MRI, secondary spondylogenic epidural abscess was diagnosed in 24 patients. At admission, the severity of neurological deficit assessed using the Frankel scale was as follows: Grade A — 6 cases, Grade B — 7 cases, Grade C — 17 cases, Grade D — 5 cases, and Grade E — 2 cases (epidural abscess without neurological deficit). At discharge, the severity of neurological deficit was as follows: Grade A — 3 cases, Grade B — 2 cases, Grade C — 13 cases, Grade D — 11 cases, and Grade E — 8 cases. In group I, 35 out of 37 patients underwent surgery; of these, 21 patients had improvement. There were no statistically significant differences in neurological deficit changes between patients with and without epidural abscess. In 12 patients, the neurological status remained unchanged. Two patients died. We present an analysis of the severity of neurological symptoms, depending on the spinal lesion level, and the results of microbiological tests. Changes in neurological symptoms in lesions of various spinal parts are described. Cervical spine lesions and the process caused by S. aureus are shown to significantly increase the risk of neurological disorders. An active surgical approach for complicated forms of spinal osteomyelitis provided partial or complete regression of neurological disorders in 62.2% of cases.

Keywords: spinal hematogenous osteomyelitis, spondylodiscitis, spondylogenic epidural abscess, neurological complications of epidural abscess.

According to the literature, there has been augmentation of the number of spinal inflammatory diseases over the past 20 years. Researches of the last decade confirmed the annual incidence of hematogenous spinal osteomyelitis from 0.2 to 2 cases per 100,000 [1, 2]. However, this value is 2.2–5.8 per 100,000 in some regions [3].

Annual morbidity increases along with aging of population and reaches a maximum in those older 80 years [4] and in high risk patients: drug addicts with parenteral intake of narcotic substances and patients with immunodeficiency. Advanced in-hospital surgical activity contributes to spread of iatrogenic spinal infections [5]. An increase of the absolute number of patients with this disease is accompanied by higher number of complicated forms.

Course of disease is uneventful as a rule. The most serious complications are systemic inflammatory response syndrome (SIRS) and secondary spondylogenic epidural abscess (SSEA) followed by neurological disorders. Incidence of these complications varies widely. A. Vishnevskiy [6] reported paresis and paralysisin 17.6%, SIRS — in 27.6% of patients. E. Pola et al. [7] found neurologically complicated epiduritis or instability in 22.4% of patients. Some authors [8, 9] reported higher incidence of neurological disorders (up to 75%) including minor sensory and motor disturbances and severe paresis and paralysis. E. Relhsaus et al. [10] analyzed 859 patients with confirmed epiduritis and found spinal osteomyelitis in only 59 (6.9%) patients. In later studies, incidence of secondary spondylogenic epidural abscess ranged from 10.0 to 34.1%. In authors’ opinion, this is due to direct spread of infectious process into spinal canal [11, 12]. Additional aspect is increased incidence of nosocomial microflora (up to 14.5%) with significant number of methicillin-resistant Staphylococcus aureus (MRSA) infection (57.1%) [13].

As a rule, delayed diagnosis of spinal osteomyelitis and its complications is associated with a potentially high risk of neurological symptoms [14]. Three Italian clinics reported mean time of diagnosis near 49.9 days [7].

Unfortunately, patients admitted to the hospitals with motor and pelvic disorders. Surgical treatment is required as a rule. However, M. Ito et al. [15] reported complete postoperative recovery in only 13.3% of patients. Patients undergo laminectomy, resection of posterior ligamentous complex, drainage of epidural and paravertebral abscesses, sanation of paravertebral soft tissues. Posterior instrumental spinal fixation is performed in patients with spinal column instability. Extended resection of anterior spinal structures can require anterior spinal fusion. Spinal osteomyelitis without epidural abscess can also result neurological deficit due to compression by soft tissues, granulations or bone structures. The potential for postoperative regression of neurological symptoms in these patients is significantly lower compared to those with epidural abscess [12, 16, 17].

Some authors [18, 19] demonstrated similar results of surgical and conservative treatment of spinal osteomyelitis. Surgical approach compared with medication is still controversial for spondylodiscitis with secondary spondylogenic epidural abscess.
The purpose of the study is to analyze the results of treatment of secondary spondylogenic epidural abscess and neurologically complicated spinal osteomyelitis.

Material and methods

There were 200 patients with spinal osteomyelitis who were treated at the Tyumen Regional Clinical Hospital No. 2 for the period 2006–2017 (department of supplicative osteology — 159 patients, neurosurgery department — 33 patients, department of suppurative surgery — 8 patients). Patients with hematogenous purulent spinal inflammation were usually in the department of suppurative osteology. Neurological deficit was an indication for hospitalization in the neurosurgical department.

Neurological symptoms were diagnosed in 37 (18.5%) patients. Grading system by H. Frankel et al. [20] was used to assess severity of neurological disorders prior to treatment and at discharge. This scale was preferred because the trial was retrospective and not all clinical observations could be assessed by the ASIA scale. All patients underwent standard clinical examination including X-ray survey at admission. Other diagnostic procedures were applied according to indications.

Consecutive X-ray examination, emergency CT and optionally MRI were carried out for uncomplicated spinal osteomyelitis. MRI prior to admission was performed in some patients that was a decisive factor in the diagnosis and hospitalization to a specialized institution. CT was used after discharge since this method is the most advisable for bone imaging.

The vast majority of patients have undergone biopsy in vertebrae under control of electron-optical transducer for the last 3 years. An exception was patients with indications for emergency surgery. The number of CT-controlled biopsies was insignificant. Standard sampling included aspiration specimen for microbiological analysis, PCR for Mycobacterium tuberculosis DNA and 1–3 bone columns for histological examination.

Eleven (29.7%) patients answered mail-sent questionnaires in more than 1 year after in-hospital treatment. These questionnaires included VAS, ND1/Oswestry, and SF36. Three patients died in the hospital. Two deaths in long-term period were not associated with spinal disease.

Statistical analysis was performed using IBM SPSS Statistics 21.0 software package. Quantitative data are presented as mean and standard deviation (M±SD). Quantitative values were compared using Mann—Whitney test due to abnormal distribution. χ2 test and Fisher’s exact test were used to identify differences between categorical variables. Neurological deficit was assessed using McNemar’s test, risk of neurological deficiency in Staphylococcus aureus infection — odds ratio. Data of visual analogue scale (VAS) before and after treatment were compared using Wilcoxon test. Differences were significant at p-value<0.05.

Results

Clinical evaluation

Neurological deficit was observed in 37 (18.5%) out of 200 patients with hematogenous spinal osteomyelitis. Mean age of patients without complications was 48.5±15.4 years, those with neurological disorders — 51.3±12.5 years. There were 3 times more men than women (148 (73.9%) vs. 52 (26.1%), respectively).

Table 1. Severity of neurological deficit (according to H. Frankel et al. classification) depending on presence of epiduritis before and after treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity of neurological disorders in patients without epiduritis before treatment</th>
<th>p*</th>
<th>Severity of neurological disorders in patients with epiduritis before treatment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>after treatment</td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>A**</td>
<td>—</td>
<td>6 (25.0)</td>
<td>0.453</td>
<td>—</td>
</tr>
<tr>
<td>C**</td>
<td>2 (15.4)</td>
<td>5 (20.8)</td>
<td>0.375</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>C**</td>
<td>6 (46.2)</td>
<td>11 (45.8)</td>
<td>0.688</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>D**</td>
<td>3 (23.1)</td>
<td>2 (8.3)</td>
<td>0.250</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>E**</td>
<td>2 (15.4)</td>
<td>5 (23.1)</td>
<td>0.385</td>
<td>5 (20.8)</td>
</tr>
</tbody>
</table>

Footnote. * — McNemar’s test — within-group comparison of values before and after treatment; ** — Fisher’s exact test; p>0.05 — between-group comparison of values before and after treatment.
### Table 4. Distribution of patients by level of spinal lesion and presence of neurological disorders

<table>
<thead>
<tr>
<th>Spinal segment</th>
<th>Course</th>
<th>No epiduritis, n (%)</th>
<th>Epiduritis, n (%)</th>
<th>Number of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative***</td>
<td>2 (100)</td>
<td>1 (50.0)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>No changes**</td>
<td>2 (40.0)</td>
<td>1 (50.0)</td>
<td>4 (80.0)</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>Positive**</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td>8 (100.0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>In all</td>
<td>9 (81.8)</td>
<td>2 (18.2)</td>
<td>11 (100.0)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Footnote.*** — χ²-test.

### Table 5. Neurological changes depending on localization of lesion

<table>
<thead>
<tr>
<th>Spinal segment</th>
<th>Course</th>
<th>No epiduritis, n (%)</th>
<th>Epiduritis, n (%)</th>
<th>Number of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative***</td>
<td>2 (100)</td>
<td>1 (50.0)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>No changes**</td>
<td>2 (40.0)</td>
<td>1 (50.0)</td>
<td>4 (80.0)</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>Positive**</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td>8 (100.0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>In all</td>
<td>9 (81.8)</td>
<td>2 (18.2)</td>
<td>11 (100.0)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Footnote.*** — Fisher’s exact test, *p* < 0.05.

### Table 6. Distribution of patients by affected spinal segment, treatment and type of stabilization procedure

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Spinal segment</th>
<th>Stabilization</th>
<th>Number</th>
<th>Stabilization</th>
<th>Number</th>
<th>Stabilization</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no</td>
<td>%</td>
<td>yes</td>
<td>%</td>
<td>yes</td>
<td>%</td>
</tr>
<tr>
<td>Sanation***</td>
<td>Cervical</td>
<td>1</td>
<td>25.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Thoracic**</td>
<td>2</td>
<td>50.0</td>
<td>2</td>
<td>66.7</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>Lumbar**</td>
<td>1</td>
<td>25.0</td>
<td>1</td>
<td>33.3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Reconstruct**</td>
<td>Cervical</td>
<td>9</td>
<td>69.2</td>
<td>4</td>
<td>36.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Thoracic</td>
<td>4</td>
<td>30.8</td>
<td>5</td>
<td>45.5</td>
<td>2</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Lumbar</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>18.2</td>
<td>1</td>
<td>18.2</td>
</tr>
<tr>
<td>Laminectomy**</td>
<td>Thoracic</td>
<td>1</td>
<td>50.0</td>
<td>2</td>
<td>100.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Lumbar</td>
<td>1</td>
<td>50.0</td>
<td>2</td>
<td>100.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>In all</td>
<td></td>
<td>19</td>
<td>—</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Footnote.*** — Fisher’s exact test, *p* < 0.05.
Patients over 50 years old accounted for 59.5% among those with complicated course of disease and 43.8% among patients with uncomplicated course of disease \( (p=0.086) \). The highest incidence of neurological complications was observed among patients aged 51—60 years \( (\text{Fig.}) \). Overall in-hospital mortality was 3.5\% \( (n=7) \), among patients with neurological deficit — 7.3\% \( (n=3) \). General signs of inflammation (fever and leukocytosis) were observed in 51.2\% of patients with neurological deficit at admission. CT was performed in 35 (94.6\%) patients with neurological complications, MRI — in 21 (56.7\%) cases. Secondary spondylogenic epidural abscess was diagnosed in 24 (64.9\%) patients with neurological deficit. Diagnostic imaging methods and intraoperative examination was used to confirm epiduritis. Secondary spondylogenic epidural abscess was diagnosed in 12\% of patients with nonspecific inflammatory spinal disease.

Frankel grade A of neurological deficit was in 6 patients at admission, grade B — in 7, grade C — in 17, grade D — in 5, grade E — in 2 patients. The same grades at discharge were in 3, 2, 13, 11 and 8 patients, respectively \( (\text{Tables} \ 1, \ 2) \). An improvement of H. Frankel grade by 22 scores was noted in 14 out of 24 patients with secondary SEA, no changes were observed in 8 cases. Two patients had aggravation of neurological deficit from grade B to grade A. Patients with neurological symptoms and no epidural abscess \( (n=13) \) were characterized by cumulative improvement by 13 scores in 8 patients. There was no dynamics in 5 cases \( (p>0.05) \).

Lesion of cervical segment occurred in 20 \( (10.0\%) \) patients, thoracic spine — 67 \( (33.5\%) \), lumbar spine — 113 \( (56.5\%) \) patients. Involvement of various spinal segments was similar among patients with neurological disorders \( (\text{Table} \ 3) \).

Lesion of cervical and thoracic spine was the most common in patients with neurological symptoms and hematogenous spinal osteomyelitis \( (\text{Table} \ 4) \).

Incidence of neurological deficit in patients with nonspecific spinal lesion is significantly increased among those with cervical spine involvement \( (p<0.001) \). Lumbar spine lesion is characterized by inverse correlation; neurological symptoms are less common. There were no significant differences in patients with thoracic spine lesion.

Dynamics of neurological disorders did not depend on the level of spinal lesion \( (\text{Table} \ 5) \).

Two unfavorable outcomes were characterized by aggravation of neurological symptoms from grade B to grade A by H. Frankel scale. Both patients had lesion of cervical spine. The third in-hospital death was observed in an advanced age patient with thoracic spine lesion and no dynamics of neurological deficit. Death was caused by postoperative multiple organ failure syndrome.

**Methods of treatment**

All procedures may be generally divided into sana
tion (drainage of intervertebral disc and/or paravertebral abscesses, vertebral sequestrectomy) and reconstructive interventions (repair of anterior spinal column support using various types of implants). Both types of interventions could be combined with spinal stabilization. Lam

ectomy is separately emphasized as the most prognosti
cally unfavorable procedure. This surgery results total instability of the spinal column and ultimately requires reconstruction. However, this intervention is performed in more difficult cases (persistent neurological deficit, microbial contamination or cicatricial deformity within spinal fixation area).

Surgical and conservative approaches were applied in 35 \( (94.6\%) \) and 2 \( (5.4\%) \) patients, respectively. Sanation, stabilization and reconstructive procedures were performed \( (\text{Table} \ 6) \).

Stabilization procedure was performed in 16 \( (45.7\%) \) patients including 3 \( (8.6\%) \) patients undergoing sanation, 11 \( (31.4\%) \) ones undergoing reconstructive surgery and 2 \( (5.7\%) \) patients — lam

inectomy. No significant differences were noted.

We did not reveal significant benefits regarding regression of neurological deficit in patients with or without spinal stabilization \( (\text{Table} \ 7) \).

However, you should pay attention that spinal fixation in spinal inflammation management significantly facilitates subsequent care and rehabilitation.

There were 16 \( (43.2\%) \) emergency surgeries on cervical spine as a rule. Duty neurosurgeon carried out these procedures. Urgent lumbar laminectomy was performed in 1 patient. Anterior approach for thoracic and lumbar spine lesion required a longer preoperative management and formation of an interdisciplinary surgical team.

**Microbiological data**

Positive results of microbiological samples were obtained in 30 \( (73.2\%) \) out of 37 patients with spinal osteomyelitis complicated by neurological disorders. Puncture of the lesion resulted positive results in 4 \( (9.8\%) \) patients. This small percentage is due to emergency surgery in patients with complicated osteomyelitis and intraoperative culture sampling as a rule. Pathogens and methods for their isolation are presented in \( (\text{Table} \ 8) \).

Epiduritis complicated by neurological deficit was commonly caused by S. aureus \( (n=13, 54.2\%) \). This value was 38.5\% among patients with neurological deficit and no epiduritis \( (\chi^2\text{-test}; p>0.05) \). Pathogen was not identified in half of cases.

Eleven \( (29.7\%) \) patients with neurological deficit filled out the questionnaires sent by mail in long-term period (over 1 year). These questionnaire included VAS, Oswestry / NDI, SF36 scales \( (\text{Table} \ 9) \).

Significant improvement of pain syndrome was observed in long-term period (range 12 months — 9 years) among patients with \( (p=0.003) \) and without neurological deficit \( (p<0.001) \). According Oswestry questionnaire data, patients with complicated course of disease had significantly worse long-term outcomes \( (p=0.036) \). Similar
tendency was confirmed in NDI scoring system ($p=0.053$).

**Discussion**

Undoubtedly, spinal osteomyelitis complicated by epidural abscess and neurological deficit requires emergency surgery. Effectiveness of treatment depends on duration of motor and sensory disorders. Long-standing neurological disorders or symptoms caused by deformation, instability or compression by granulation tissue are more resistant for treatment. Character and urgency of intervention vary significantly in these cases. Vertebral resection with dural sac decompression should be necessarily followed by reconstruction and stabilization procedures. We did not reveal any significant benefits of spinal stabilization regarding neurological deficit regression. However, spinal fixation greatly facilitates postoperative care. Anterior reconstruction results a reliable bone block and stable correction of deformity [21].

The majority of patients with neurological disorders underwent surgical treatment. Active surgical strategy resulted positive neurological dynamics in 62.2% of patients at discharge. Only 2 (5.4%) patients had aggravation of neurological deficit. Both patients had cervical spine lesion and died in the hospital due to aggravation of neurological deficit.

There is a question regarding urgency and type of surgical intervention, composition of surgical team. A. Tschugg et al. [22] reported open surgical technique as more effective for spondylodiscitis complicated by epidural abscess.

Minimally invasive techniques should be applied very carefully in some cases, but it is possible even for epiduritis.

A. Boström et al. [23] reported key role of minimally invasive drainage procedures aimed at isolation of the pathogen and dural sac decompression. However, need for spinal stabilization should be individually discussed for pathological fracture of the vertebrae. In our opinion, secondary SEA requires spinal cord decompression (anterior as a rule) through resection of anterior vertebral structures. Spinal stabilization is an important surgical stage, although it may be delayed in some cases.

We prefer two separate surgical procedures for spinal lesion below cervical segment (repair of the anterior structures and posterior stabilization of adjacent vertebrae). Lesion of one vertebral segment may be rigidly fixed by a four-screw system considering intact posterior column.

Table 8. Frequency of detection of various pathogens in patients with complicated spinal osteomyelitis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Intraoperative microbiological examination, n (%)</th>
<th>Puncture of the lesion</th>
<th>Blood sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus (MSSA)</em></td>
<td>18 (48.6%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus (MRSA)</em></td>
<td>1 (2.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>Staphylococcus epidermis</em></td>
<td>3 (8.1)</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Clostridium spp.</td>
<td>2 (5.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>2 (5.4)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peptococcus</td>
<td>1 (2.7)</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td><em>Staphylococcus saprophiticus</em></td>
<td>1 (2.7)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1 (2.7)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1 (2.7)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Bacteroides spp.</td>
<td>1 (2.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acinetobacter hoffii</td>
<td>1 (2.7)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 9. Long-term outcomes of complicated and uncomplicated hematogenous spinal osteomyelitis (VAS, Oswestry/NDI and SF36 scales)

<table>
<thead>
<tr>
<th>Scale</th>
<th>n</th>
<th>Without neurological deficit</th>
<th>n</th>
<th>With neurological deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M±SD Median (25—75%)</td>
<td></td>
<td>M±SD Median (25—75%)</td>
</tr>
<tr>
<td>VAS score prior to treatment</td>
<td>54</td>
<td>8.4±2.34 9.0 (8.0—10.0)</td>
<td>11</td>
<td>7.9±2.30 8.0 (6.0—10.0)</td>
</tr>
<tr>
<td>VAS score after treatment</td>
<td>54</td>
<td>2.3±1.81 2.0 (1.0—3.0)</td>
<td>11</td>
<td>1.8±1.72 2.0 (0—4.0)</td>
</tr>
<tr>
<td>Oswestry</td>
<td>52</td>
<td>18.6±15.61 17.8 (6.0—26.0)</td>
<td>6</td>
<td>33.9±23.97 38.0 (12.0—51.1)</td>
</tr>
<tr>
<td>NDI (scores)</td>
<td>2</td>
<td>21.5±4.95 21.5 (18.0—25.0)</td>
<td>5</td>
<td>5.2±3.11 6.0 (5.0—7.00)</td>
</tr>
<tr>
<td>SF36 — PH (physical health)</td>
<td>52</td>
<td>38.8±9.67 36.8 (30.7—46.5)</td>
<td>11</td>
<td>37.9±11.51 32.9 (30.0—47.8)</td>
</tr>
<tr>
<td>SF36 — MH (mental health)</td>
<td>52</td>
<td>46.9±9.92 46.9 (40.1—54.2)</td>
<td>11</td>
<td>49.3±14.01 52.5 (35.3—60.5)</td>
</tr>
</tbody>
</table>

E. Pola et al. [7] analyzed 250 patients with spondylodiscitis. The group of epidural abscess and/or neurological deficit consisted of 120 patients. Only 56 (22.4%) of these patients had neurological disorders. Conservative approach was applied in 64 patients with epidural abscess with or without segmental instability. Indications for conservative therapy were significantly enlarged in this research. There were 115 (46%) patients after surgery. Minimally invasive percutaneous stabilization was performed in 19 (7.6%) of them in order to increase patient’s mobility. It was emphasized that spontaneous bone block occur within 6—24 months.

**Conclusion**

Hematogenous spinal osteomyelitis is a rare disease and characterized by delayed diagnosis. Secondary spondylogenic epidural abscess significantly worsens the prognosis for this disease. Cervical spine lesion increases the risk of neurological disorders.

Active surgical approach for complicated spinal osteomyelitis was followed by partial or complete regression of neurological disorders in 62.2% of cases.

Multiple-center study is advisable due to the rarity of non-specific spinal lesions and those complicated by neurological deficit. So, aggregation of clinical data from various clinics experienced in the treatment of secondary spondylogenic epidural abscess may be recommended.

**Authors declare no conflict of interest.**
The report is devoted to the problem of complicated supplicative spinal lesions. In particular, non-specific secondary spinal osteomyelitis followed by supplicative epiduritis (epidural abscess) is being considered.

The authors combined an experience of several medical institutions of the Tyumen region. They also justified advisability of early surgery in patients with neurological deficit through assessment of neurological status and emergency decompression and stabilization interventions.

Currently, the problem of osteomyelitis/vertebral spondylodiscitis involving spinal sheaths has clear epidemic signs for megalopolises. Increased life expectancy in cities, great number of patients with immunodeficiency and active surgical approach in advanced age patients with osteoporosis and severe spinal degeneration resulted wide prevalence of acute epidural purulent complications requiring emergency surgery. At the same time, preferable elective surgery and insufficient attention to the development of neurological deficit caused by suppuration resulted the fact that neurosurgeons and osteologists overlook these patients.

The authors reported an algorithm for determining treatment strategy depending on the level of lesion. Thus, they reasonably propose bilateral approach for lesion below cervical segment. Transpedicular stabilization outside the focus of purulent inflammation is preferred for spinal instability if vertebral focal lesion results ventral compression (90% of cases). Differentiated strategy and conservative treatment depending on certain pathogen (S. aureus including MRSA as a rule) are also discussed.

Undoubtedly, treatment of infectious spinal disease complicated by neurological symptoms is a difficult problem. There are no disagreements regarding medication and antibacterial, specific, immunocorrective and restorative agents are recognized as effective and widely used in clinical practice. Blind untimely medication with antibiotics is ineffective. Therefore, multiple blood samples, biopsy confirmed by histological examinations are advisable prior to treatment. The majority of researchers recommend therapy if vertebral destruction and spinal cord compression are not confirmed by X-ray examination.

Spinal osteomyelitis with epidural spread is easily amenable to antibiotic therapy at the early stages. However, surgical treatment is inevitable for neurological disorders, spinal instability and epidural abscess in case of late diagnosis, sepsis and progression of the disease despite adequate antibiotic therapy. Surgery usually consists of sanation of purulent lesion and spinal stabilization if it is necessary. Surgical treatment is contraindicated in patients with severe vascular diseases. Contraindications for surgical treatment are also sepsis and severe concomitant diseases because high risk of death is observed in these cases. These patients require comprehensive therapy.

This report is useful for specialists in spinal and supplicative surgery.

A.O. Gushcha (Moscow, Russia)
Arteriovenous malformations and epileptic seizures in children: risk factors of seizures and efficacy of their control depending on the surgical treatment modality

A.R. Tadevosyan*, K.V. Sysoev, K.A. Samochernykh, V.A. Khachatryan

Almazov National Medical Research Center, Saint Petersburg, Russia

Epileptic seizures are some of the most frequent manifestations of cerebral AVMs in children. Poor control of seizures can significantly affect patients’ quality of life. In this case, factors that are associated with the development of seizures and affect the efficacy of their control upon treatment of cerebral AVMs are not well understood.

Purpose. The purpose of this study was to identify risk factors for the development of epileptic seizures as well as factors associated with a seizure-free outcome of AVM treatment in children.

Material and methods. We analyzed the results of examination and treatment in 89 patients with cerebral AVMs aged 1 to 17 years.

Results. Factors associated with the development of epileptic seizures in cerebral AVMs in children included male gender of the child, a large size of AVM and its superficial location, as well as localization of the pathology in the frontal and temporal lobes of the brain and draining varices. Regression of seizures after surgery was more often observed in the case of microsurgical and/or complex surgical treatment and complete exclusion of the AVM as well as in cases of rare attacks and a short course of the disease.

Conclusion. Complex and microsurgical treatment of AVMs in children provides effective control of epileptic seizures, which is obviously associated with complete exclusion of the AVM and removal of the epileptic focus located near the AVM.

Keywords: AVM, epileptic seizure, treatment.
seizures was noted in 18 (81.82%) patients receiving single drug therapy. Five patients required additional administration of the second drug. Nevertheless, seizures were completely controlled only in 2 cases. Epileptic seizures were much more common in boys \((p=0.024)\) and in children younger than 7 years \((p=0.044)\). Diffuse EEG changes were diagnosed in 6 (18.75%) patients, local slow-wave activity on the background of diffuse changes — in 7 (21.88%) patients, local paroxysmal activity on the background of diffuse changes — in 19 (59.38%) patients.

It was found that risk of epileptic seizures is higher in patients with large AVM. Right- or left-sided localization of AVM was not a significant predictor of seizures. However, superficial AVM was significantly associated with the development of seizures \((p=0.00027)\). Epileptic seizures were often caused by frontal \((p=0.027)\) and temporal \((p=0.047)\) AVMs. Blood supply of AVM from the middle cerebral artery \((p=0.03)\) and local varicose veins \((p=0.046)\) were reliably associated with epileptic seizures.

Early postoperative seizures de novo occurred in 3 patients. In one case, seizures were generalized tonic-clonic and appeared after clipping and partial removal of AVM. Partial seizures were diagnosed in 2 patients (during embolization in 1 case and in 2 days after EVE in the other case). Recurrent postoperative epileptic seizures occurred in 14.28% of patients. Three patients had paroxysmal seizures in 1—2 days after EVE, 1 patient — in 2 days after removal of AVM and intracerebral hematoma. There were seizures in long-term period after clipping and partial removal of AVM in 1 child. Redo surgery resulted more frequent seizures in this case. However, correlation between surgical treatment modality and early postoperative seizures was insignificant \((p_{2\text{-tailed}}=0.707)\). Early seizures after embolization were commonly observed in patients with a large AVM \((p_{2\text{-tailed}}=0.061)\) and after Onyx18 embolic agent injection \((p_{2\text{-tailed}}=0.023)\).

Complete regression of seizures was noted in 15 (46.9%) out of 32 patients, improvement — in 24 (75%) out of 32 patients. No significant changes were observed in 6 (18.75%) out of 32 patients. Engel grades of the out-

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**Table 1. Surgical procedures in patients with AVM**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>No seizures, % (n=57)</th>
<th>With seizures, % (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVE*, SRS**</td>
<td>43.86 (25)</td>
<td>53.12 (17)</td>
</tr>
<tr>
<td>Hematoma evacuation</td>
<td>5.26 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Removal of hematoma and AVM</td>
<td>7 (4)</td>
<td>6.25 (2)</td>
</tr>
<tr>
<td>Removal of AVM</td>
<td>53.2 (25)</td>
<td>9.38 (3)</td>
</tr>
<tr>
<td>Removal of AVM and arachnoid cyst</td>
<td>0 (0)</td>
<td>6.25 (2)</td>
</tr>
<tr>
<td>Removal of AVM and epileptic focus</td>
<td>0 (0)</td>
<td>15.63 (5)</td>
</tr>
<tr>
<td>Removal of AVM, epileptic focus and subpial transections</td>
<td>0 (0)</td>
<td>6.25 (2)</td>
</tr>
<tr>
<td>Subpial transections and amygdalohypopacompectomy, without removal of AVM</td>
<td>0 (0)</td>
<td>3.13 (1)</td>
</tr>
</tbody>
</table>


---

**Table 2. Distribution of patients depending on age and gender**

<table>
<thead>
<tr>
<th>Variable</th>
<th>In all. % (n)</th>
<th>No seizures 64.1% (n=57)</th>
<th>With seizures 35.95% (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age. years ((M±SD))</td>
<td>10.4±3.88</td>
<td>10.5±3.8</td>
<td>10±4.1</td>
</tr>
<tr>
<td>Younger 7 years</td>
<td>22.5 (20)</td>
<td>15.8 (9)</td>
<td>34.4 (11)</td>
</tr>
<tr>
<td>8—17 years</td>
<td>77.5 (69)</td>
<td>84.2 (48)</td>
<td>65.6 (21)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>52.8 (47)</td>
<td>43.9 (25)</td>
<td>68.8 (22)</td>
</tr>
<tr>
<td>F</td>
<td>47.2 (42)</td>
<td>56.1 (32)</td>
<td>31.3 (10)</td>
</tr>
</tbody>
</table>

---

**Table 3. Engel grade of the outcomes depending on surgical treatment modality**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Surgical procedure</th>
<th>MS</th>
<th>EVE</th>
<th>EVE+MS</th>
<th>EVE+STS</th>
<th>EVE+MS+STS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, n (%)</td>
<td>4 (80)</td>
<td>4 (25)</td>
<td>6 (75)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>II, n (%)</td>
<td>1 (20)</td>
<td>7 (43.75)</td>
<td>1 (12.5)</td>
<td>1 (50)</td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td>III, n (%)</td>
<td>0 (0)</td>
<td>4 (25)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>0 (0)</td>
<td>1 (6.25)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>In all</td>
<td>5 (15)</td>
<td>16 (50)</td>
<td>8 (25)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Footnote. MS — microsurgery, STS — stereotactic radiosurgery, EVE — endovascular embolization.
Fig. 1. Kaplan-Meier curve of cumulative disease-free period (with 95% CIs) for more than 2 years after microsurgical or endovascular treatment of AVM.

Fig. 2. a, b — Endovascular embolization of AVM; c — fMRI-scan: localization of the Broca’s area; d — MR-spectroscopy: increased concentration of lactate (arrow); e — PET: no accumulation of 18-FDG in AVM and significant decrease in the brain tissue around AVM; f, g, h — EEG-monitoring before (f) and after (h) removal of the epileptic focus.

Explanations in the text.
comes depending on surgical procedure are shown in Table 3. Microsurgical removal of AVM resulted more adequate and earlier control of epileptic seizures compared with endovascular occlusion (p=0.0024) (Fig. 1).

Case report
An 8-year-old patient with AVM in the left frontal lobe suffered frequent secondary-generalized epileptic seizures. The first surgical stage was partial embolization of AVM with histoacryl (Fig. 2a, b). Persistent seizures required an additional examination. Close proximity of AVM to the Broca’s area was confirmed using functional MRI (Fig. 2c). MRI-spectroscopy revealed increased concentration of lactate (a sign of ischemia) and reduced concentration of N-acetylaspartate (a sign of decreased neuron density). Positron emission tomography (PET) with 18-FDG revealed no accumulation of 18-FDG in AVM and significant decrease in perifocal brain tissue (Fig. 2d, e). The second stage of surgical treatment was microsurgical removal of the epileptic focus under EEG control (Fig. 2, f–h). There was a significantly reduced incidence of seizures after surgery.

Epileptic seizures are diagnosed in 30% of children with cerebral AVM on the average [5–8]. It is known that long-standing disease results gradually increase of the incidence of seizures and their resistance to medication [9]. Epileptic foci become more stable and complex epileptic system is formed with the appearance of new foci. These features reduce the likelihood of elimination of the foci and worsen outcomes.

In our sample, epileptic seizures were the initial manifestation of disease in 17 (19.1%) out of 89 patients. Our results are similar to those available data regarding higher incidence of epileptic seizures in males. Risk of seizures was significantly higher in children younger 7 years old. As expected, superficial localization of AVM and lesion of potentially more epileptic cerebral areas (frontal and temporal lobes) were reliably associated with manifestation of AVM with epileptic seizures. There were no seizures in patients with AVM of posterior cranial fossa, basal ganglia, and brain ventricles. Risk of epileptic seizures was up to 50% in case of AVM diameter ≥55 mm that is probably due to significant steal and ischemia of the adjacent areas. Our data are consistent with well-known risk factors of seizures in children with AVM such as large dimension of malformation and localization in the frontal lobe [7].

Early postoperative seizures may be associated with surgical trauma and edema after microsurgical procedure and ischemic changes after endovascular occlusion. Seizures in long-term period after EVE are more easily controlled or recover compared with those after microsurgical treatment. Recurrent epileptic seizures in early postoperative period with changes of their incidence, structure and EEG pattern (compared with preoperative data) may indicate the appearance of new epileptic foci. In general, early postoperative seizures were more common after endovascular occlusion of AVM using Onyx18 compared with histoacryl. This may be due to toxic effects and development of perifocal edema. Recent studies [7] have shown that the effectiveness of surgical treatment regarding epileptic seizures control is influenced by degree of AVM occlusion. In our study microsurgical procedure was more effective for epileptic seizures control than EVE (p=0.03). Earlier achievement of favorable outcome was noted (p=0.0024). Microsurgical intervention resulted positive effect immediately after surgery. This may be associated with simultaneous removal of AVM and epileptic focus [10, 11]. Degree of AVM occlusion also significantly influenced the outcomes besides surgical technique. Complete occlusion was significantly correlated with Engel grade I outcome (p<0.0001). Rare seizures (p=0.027) and seizures with short history (p=0.049) were more effectively controlled.

Thus, an obvious advantage of microsurgical treatment of AVM followed by epileptic seizures is a complete single-stage occlusion of AVM and possible additional verification and removal of the epileptic focus. It should be noted that epileptogenic focus does not always coincide with the localization of AVM considering structure of seizures and EEG data. AVM in temporal lobe often results epileptic foci in mediobasal areas of the hemisphere. At the same time, concomitant abnormalities (arachnoid cysts, focal cortical dysplasia, etc.) may also contribute to the development of seizures. In our opinion, comprehensive preoperative examination, analysis of seizures structure and intraoperative assessment of EEG are essential to verify and remove additional epileptic foci and improve the outcomes. It is especially true if patients with seizures unresponsive to anticonvulsant therapy are scheduled for microsurgical treatment.

Authors declare no conflict of interest.

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https://doi.org/10.1007/BF03009913


Comment

The relevance of the issue is not in doubt. Optimal treatment strategy for AVM followed by epileptic seizures (ES) is still unclear despite many years of discussion of this question. Pediatric surgery for AVM is especially difficult problem significantly influencing decision-making.

The authors analyze 32 patients with AVM followed by ES who were treated in the Polenov RRNS for 17 years. There are two main parts in the work: the first is an analysis of risk factors of ES in patients with AVM. The second is assessment of the effect of interventional treatment (microsurgery, radiosurgery, endovascular treatment) on the course of epilepsy.

The first question is considered using comparison of AVM patients with ES and those without seizures. The authors identify the factors associated with ES and confirm well-known data about the preferential development of ES in patients with large cortical frontal and temporal AVMs. Incidence of ES is also similar to that described in the literature (approximately 30% of patients). Unfortunately, it is not clear whether there were AVM-associated hemorrhages in 32 patients. It seems to be that hemorrhages occurred if the authors report ES as the first manifestation only in 17 patients. However, this question is not discussed at all, although it is very important regarding indications for surgery. Can single ES determine diagnosis of epilepsy especially in case of simultaneous hemorrhage? It is not clear which criteria were used to determine the “varicose veins” of AVM. At the same time, this feature was defined as risk factor of epileptic syndrome.

Postoperative freedom from seizures are generally similar to that reported in the literature (75% of patients with improvement, 46% without seizures). However, incomplete analysis of data raises a number of questions. For example, localization and dimensions of AVMs, Spetzler—Martin grades are not given. There is also no analysis of the completeness of removal and/or degree of obliteration of AVM after various interventions. Comparison of pre- and postoperative neurological deficit is not shown. The authors do not describe structural features of the perifocal area and criteria determining extent of its excision especially in patients without hemorrhage and those with AVM in functionally significant zone. Indications for additional antiepileptic surgeries in 8 patients, in particular for amygdalohypaccpectomemy and transections without AVM removal in 1 patient (Table 1). Judgments about persistent epileptic foci and distant foci de novo are not substantiated, in particular information about new epileptic foci after surgery. Incidence of postoperative seizures is quite high in patients without these disturbances prior to surgery (about 7%). Engel grade outcomes are presented, but there are no preoperative characteristics regarding this grading system. Therefore, comparison of these data is difficult.

The article is of great interest despite all above-mentioned remarks. It is especially true for data analysis system. The research is valuable for discussion of modern approaches to evaluation of clinical scientific data. The problem of reliability of clinical data has been widely discussed in recent years. Moreover, this question became especially relevant in the treatment of AVM after ARUBA trial publication [1, 2].

O.B. Belousova (Moscow, Russia)

REFERENCES

The research is devoted to the effectiveness of surgical treatment of AVM in children with epileptic seizures as one of the most frequent clinical symptom. Incidence of symptomatic epilepsy resistant to antiepileptic drug therapy among patients with AVMs was similar to that in previous reports (30%). Significant predictors of epileptic seizures were localization of AVMs (frontal and temporal lobes), their dimensions (large), donor pool (MCA) and overloaded varicose drainage veins.

It is known that total resection or obliteration of AVM usually result favorable outcomes and elimination of seizures. It is clear that radical excision or complete occlusion of malformation was not possible in every case. There are no data about types of resection, but correlation of postoperative seizures and surgical technique is analyzed (microsurgical resection, endovascular occlusion and stereotactic radiosurgery or their combination). Microsurgical resection was the most effective (4 out of 5 patients).

Obviously, long-standing structurally determined symptomatic focal seizures result resistant epileptogenic zone in perifocal cerebral area without structural abnormalities. Electroconvulsive therapy and limited cortical resection are able to eliminate seizures or reduce their frequency and severity in some cases. These interventions require experience in surgery of epilepsy that is demonstrated by the authors in this report.

A.G. Melikyan (Moscow, Russia)
According to various data [1], about 40% of children with pharmacoresistant symptomatic epilepsy have cerebral cortex malformations. Focal cortical dysplasia (FCD) is the most common cause of pharmacoresistant epilepsy in children [2]. This diagnosis is verified by intraoperative neuromorphological examination. Surgery is one of the approaches for the majority of these patients [3].

Quality of preoperative examination significantly determines surgical outcomes [4, 5]. The main objectives of preoperative examination are localization and determination of the boundaries of the epileptogenic zone [6], i.e. cortical area responsible for seizures. Removal of this area results disappearance of seizures [7]. Preoperative examination requires a multimodal approach. Leading role belongs to long-term video-EEG-monitoring (VEM) [3, 8, 9].

A long-term VEM is useful to analyze semiology of seizures, interictal and ictal EEG data, to differentiate seizures and non-epileptic events, to classify seizures and to determine localization of epileptic focus. Interpretation of focal interictal epileptic activity gives useful information about localization of the focus [3]. Complete removal of epileptogenic area is essential for favorable surgical outcome. Assessment of ictal EEG changes is very important to localize the focus [6—8]. Interictal activity corresponds to epileptic area in some cases [10]. However, it is not always true and ictal EEG changes are considered more significant for localization of epileptogenic area [11, 12].

There is no a single standard regarding certain EEG activity as ictal pattern (IP) onset [13, 14]. Detection of EEG changes characteristic for IP onset may be an auxiliary material for verifying seizures and localizing the epileptogenic zone. Evolution over time is one of the signs of epileptic seizure. Therefore, it is important to evaluate combinations of transitions from one activity to another.

The purpose of the study is to identify the features of IP onset on scalp EEG depending on histology, localization and spread of epileptogenic lesion, to determine correlation of the concordance of localization of interictal and ictal activity with types of IP onset.

The study group included 38 patients with neuro-morphologically verified FCD. All patients underwent surgical treatment of pharmacoresistant epilepsy in the Burdenko Neurosurgery Center for the period 2010—2016. There were 22 boys and 16 girls aged from 6 months to 15 years (median 3 years). Each patient underwent 3—120-hour-long-term video-EEG-monitoring, multichannel EEG in the frequency range 1—70 Hz (Ni-colet One system, USA; 44 and 128 channels). Electrodes
were arranged according to the International scheme 10—20%. ECG and zygomatic electrodes were deployed if it was necessary.

Neurosurgical interventions included resection of FCD within one or several brain lobes and hemispherectomy for advanced hemispheric lesion.

Areas of interictal and ictal EEG activity were identified and analyzed. Interictal activity and IP onset were identified visually by at least two specialists in all cases. Disagreements were resolved through discussion and consensus. The following types of interictal activity were considered: sharp, slow waves; complexes: sharp-slow wave, spike-wave, spike, polyspike. Isolated and combined types of interictal activity could be observed in each specific case.

IP was retrospectively evaluated within 10 s after beginning. IP reliability was confirmed by clinical manifestations typical for certain patient. Therefore, IPs were divided into types and variants.

Correlations of the area of IP and interictal activity, as well as different types of IP onset and types of FCD were analyzed. Types of FCD were identified according to the classification proposed by the International League against Epilepsy in 2011 (Table 1) [6]. Localization and spread of IP in groups with different types of its onset were assessed.

### Table 1. Classification of focal cortical dysplasias (International League against Epilepsy, 2011)

<table>
<thead>
<tr>
<th>FCD type I (isolated)</th>
<th>FCD with abnormal radial dyslamination of the neocortex (FCD type Ia)</th>
<th>FCD with abnormal tangential dyslamination of the neocortex (FCD type Ib)</th>
<th>FCD with abnormal radial and tangential dyslamination of the neocortex (FCD type Ic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCD type II (isolated)</td>
<td>FCD with dysmorphic neurons (FCD type IIa)</td>
<td>FCD with dysmorphic neurons and balloon cells (FCD type IIb)</td>
<td></td>
</tr>
<tr>
<td>FCD type III (combined with major lesion)</td>
<td>Abnormal neuronal dyslamination in temporal lobe with hippocampal sclerosis (FCD type IIIa)</td>
<td>Abnormal neuronal dyslamination adjacent to glial or glioneuronal tumor (FCD type IIIb)</td>
<td>Abnormal neuronal dyslamination with any early acquired lesion (trauma, ischemic injury, encephalitis) (FCD type IIId)</td>
</tr>
</tbody>
</table>

Fig. 1. IP onset as electrodecrement followed by rhythmic local activity.
EEG. Observation 4 (Table 2). Analysis within 10 s after electroencephalographic changes onset. Recording variables: bipolar mode, speed 20 mm/s, amplitude 200 μV/cm, frequency range 70.0—1000 Hz, surge protector 50 Hz.
Non-parametric statistical analysis was used to assess reliability of data (cross tabulation, $\chi^2$ test).

**Results**

Ictal activity was rhythmic as a rule and observed as grouped sinusoidal or sharp oscillation. Two types of IP onset were identified: local and generalized. Signs of activity in more than 4 leads determined generalized pattern, in 1–4 adjacent leads — local IP.

Local rhythmic activity at the beginning of IP was recorded in patients with local IP (group 1). Patients with generalized onset of IP (group 2) were characterized by diffuse electrodecrement. Disappearance of interictal activity or appearance of diffuse or generalized rhythmic epileptiform activity with generalized patterns could precede diffuse electrodecrement.

Various features of IP within 10 s after onset were comprehensively analyzed. Two and four variants of rhythmic activity were identified in patients with local and generalized types of IP onset, respectively.

**EEG data in local type of IP onset**

1. Electrodecrement with subsequent local rhythmic activity was observed in 10 (26.3%) patients (Fig. 1).
2. Local rhythmic oscillations were noted in 10 (26.3%) patients (Fig. 2).

**EEG data in generalized type of IP onset**

1. Electrodecrement with subsequent rhythmic generalized activity was recorded in 7 (18.5%) patients (Fig. 3).
2. Diffuse flattening of rhythm in 7 (18.5%) patients.
3. Single impulse with subsequent flattening of rhythm in 3 (7.8%) patients.
4. No EEG changes in 1 (2.6%) patient

Observation No. 38 (Table 2, a 12-year-old boy). Aura prior to seizures manifested with a “feeling of excitement” and was not followed by clear EEG changes. According to MRI data, there was a focus in the medial cortex of the right occipital lobe. Postoperative neuro-morphological examination revealed FCD type IIIb. Postoperative seizures have not been diagnosed since 2013 (outcome Engel grade Ia).

Analysis of FCD types, localization of lesion, coincidence of localization of interictal and ictal activity, features of IP onset are shown in Table 2.

Similar areas of ictal and interictal activity were observed in 16 (42%) patients. Local IP was noted in 88% of these patients. Areas of ictal and interictal activity did not coincide in 22 (58%) patients and patients with generalized type of IP onset prevailed (76%).

Non-parametric statistical methods were used to analyze coincidence or non-coincidence of the areas of ictal and interictal activity. $\chi^2$ test was 0.0001.
There were following correlations of FCD types and IP onset. Patients with FCD types I and III had diffuse flattening of rhythm as a rule (40 and 30% of patients, respectively). In patients with FCD type II, ictal activity onset in form of local rhythmic oscillations both independently (39%) and after electrodecrement prevailed (33%). Data are presented in Table 3. Localization of lesion and its spread (involvement of one or several adjacent brain lobes) were evaluated for each type of pattern (Table 2) with local and generalized onset. Thirteen patients with generalized type of IP onset had lesion of one lobe of the brain, 5 patients — involvement of several lobes. Lesion of one lobe of the brain was noted in 15 patients with local type of IP onset, involvement of several lobes— in 5 patients.

There was no significant predominance of certain type of activity depending on localization of lesion. Thus, localization and spread of cerebral lesion did not significantly correlate with the type of IP onset.

Assessment of surgical area in preoperative diagnosis of epilepsy has been repeatedly discussed in the literature [3, 7, 9, 15—17]. A comprehensive approach is necessary for FCDs because various diagnostic methods [3, 5, 9] are characterized by certain limitations. For example, MRI-based diagnosis of FCD is not always reliable, because inadequate information regarding dimension and localization of dysplasia may be obtained [18, 19]. MR-negative FCDs are observed in 23% of cases (FCD type 1 as a rule) [5, 20]. VEM has an essential role in assessment of localization and spread of lesion. However, interpretation of interictal data is difficult and sometimes ambiguous. According to the literature [21, 22], medial occipital and medial frontal epilepsy may be associated with bilateral, generalized epileptiform discharges and contralateral interictal epileptiform activity. In 30% of patients with temporal epilepsy, bitemporal interictal epileptiform activity is diagnosed while the area of IP onset is usually lateralized [23]. Interictal epileptiform activity may be absent in approximately 10% of patients with temporal epilepsy and in 1/3 of patients with frontal epilepsy [22, 24]. Literature data confirm that interictal activity is more spread in VEM that area of IP onset.

Accurate localization of trigger area is extremely important for successful surgical treatment. However, discharges of epileptiform activity are often observed on the background of no clinical symptoms of seizures while EEG changes may be absent at initial symptoms of seizures. Changed EEG biopotentials may be invisible due to artifacts. Difficult interpretation of clinical events is also caused by behavioral patterns in childhood [2, 7, 14].

About 2/3 of cerebral cortex is located deep in the furrows and dipole of discharge is not always projected on the scalp. Trigger zone may be localized in medial-temporal, orbital-frontal and inter-hemispheric areas at a large distance from scalp electrodes. As a result, IP onset is not fixed and it is only possible to register the moment

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**Fig. 3.** IP onset as electrodecrement followed by a rhythmic generalized activity.

EEG. Observation 26 (Table 2). Recording variables: bipolar mode, speed 30 mm/s, amplitude 200 μV/cm, frequency range 70.0—1600 Hz, surge protector 50 Hz.
### Table 2. Type and localization of lesion, coincidence of the localization of interictal and ictal activity, features of IP onset

<table>
<thead>
<tr>
<th>№</th>
<th>Sex/age of patient</th>
<th>FCD type</th>
<th>Localization</th>
<th>Coincidence of the areas of interictal and ictal patterns</th>
<th>Features of IP onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G, 8 months</td>
<td>Ic</td>
<td>P.O.T</td>
<td>–</td>
<td>Electrodecrement followed by rhythmic local pattern</td>
</tr>
<tr>
<td>2</td>
<td>B, 10 months</td>
<td>IIa</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>G, 3 years 11 months</td>
<td>IIb</td>
<td>T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>B, 8 years</td>
<td>IIa</td>
<td>T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>G, 11 months</td>
<td>IIa</td>
<td>P.O.T</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>B, 13 years</td>
<td>IIIa</td>
<td>T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>B, 8 years</td>
<td>IIIa</td>
<td>T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>B, 6 months</td>
<td>IIb</td>
<td>P.O.</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>G, 6 years</td>
<td>IIa</td>
<td>O.T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>G, 2 years 2 months</td>
<td>IIa</td>
<td>O</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>B, 2.5 d years</td>
<td>Ic</td>
<td>H</td>
<td>+</td>
<td>Rhythmic local oscillations</td>
</tr>
<tr>
<td>12</td>
<td>G, 1 year</td>
<td>IIa</td>
<td>H</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>G, 2 years 3 months</td>
<td>IIa</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>G, 3 years</td>
<td>IIa</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>B, 9 years</td>
<td>IIb</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>G, 4 years</td>
<td>IIb</td>
<td>P</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>G, 5 years</td>
<td>IIb</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>G, 2 years 5 months</td>
<td>IIb</td>
<td>H</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>B, 10 years</td>
<td>IIId</td>
<td>P.O.T</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>B, 3 years</td>
<td>IIId</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>G, 1.9 years</td>
<td>Ic</td>
<td>H</td>
<td>–</td>
<td>Electrodecrement followed by rhythmic generalized activity</td>
</tr>
<tr>
<td>22</td>
<td>B, 2 years 11 months</td>
<td>Ic</td>
<td>F</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>B, 2 years 3 months</td>
<td>IIa</td>
<td>P.T</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>G, 8 years</td>
<td>IIb</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>B, 7 years</td>
<td>IIb</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>G, 3 years</td>
<td>IIb</td>
<td>P.T</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>B, 1 year 3 months</td>
<td>IIb</td>
<td>P</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>B, 6 months</td>
<td>Ia</td>
<td>F.T</td>
<td>–</td>
<td>Diffuse flattening of rhythm</td>
</tr>
<tr>
<td>29</td>
<td>B, 7 years</td>
<td>Ic</td>
<td>P.O</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>B, 5 years</td>
<td>Ic</td>
<td>P.O</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>G, 3 years</td>
<td>Ic</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>B, 14 years</td>
<td>IIIa</td>
<td>T</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>B, 15 years</td>
<td>IIIb</td>
<td>T</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>B, 13 years</td>
<td>IIId</td>
<td>F</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>B, 2 years 11 months</td>
<td>IIb</td>
<td>P</td>
<td>–</td>
<td>Single impulse with subsequent flattening of rhythm</td>
</tr>
<tr>
<td>36</td>
<td>G, 3 years</td>
<td>IIb</td>
<td>P</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>B, 2 years</td>
<td>IIId</td>
<td>H</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>B, 12 years</td>
<td>IIIb</td>
<td>O</td>
<td>–</td>
<td>No clear EEG changes</td>
</tr>
</tbody>
</table>


### Table 3. Distribution of patients with different types of FCD depending on features of IP onset

<table>
<thead>
<tr>
<th>FCD type</th>
<th>Number of patients (100%)</th>
<th>Electrodecrement followed by rhythmic local pattern, %</th>
<th>Electrodecrement followed by rhythmic generalized activity, %</th>
<th>Local rhythmic oscillations, %</th>
<th>Diffuse flattening of rhythm, %</th>
<th>Single impulse with subsequent flattening of rhythm, %</th>
<th>No clear EEG changes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>3 (30)</td>
<td>2 (20)</td>
<td>1 (10)</td>
<td>4 (40)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>6 (33)</td>
<td>4 (22)</td>
<td>7 (39)</td>
<td>0</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>2 (20)</td>
<td>1 (10)</td>
<td>2 (20)</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

72
of its projection on the scalp. It is known that EEG bio-

potentials prior to seizure or those coinciding with clini-

cal event are the most reliable ictal EEG manifestations.

Ictal activity can involve various zones including remote
cerebral areas [25].

Variants of IP onset in various pathologies have al-

ready been described in the literature [14]. Morphology

and frequency characteristics of bio potentials were ma-

inly considered (rhythm frequency changes in theta-delta-

alpha range, rhythm spikes, spike-wave complexes, high-frequency activity). Various patterns were analyzed in patients with FCD using scalp EEG and electrocorti-

cograms [3, 26]. However, there are still no clear defini-
tions of preictal, ictal and postictal activity. Therefore,
certain difficulties accompanying distinguishing these pat-
tterns have been described in the literature [14].

In this study, an important role in assessment of epi-

leptiform activity is given to the features of IP onset and

rhythm evolution over time. We identified 2 types and

6 variants of combinations of cortical rhythmic changes.

The majority of patients with FCD type II had local

rhythmic oscillations at the beginning of IP, those with

FCD types I and III - diffuse flattening of rhythm. It was

confirmed by invasive examinations [27]. FCD type II is

characterized by severe disorders of cortical architecture

that result active processes of epileptogenesis and rhyth-
mic epileptiform activity.

Perhaps, predominance of patients without coinci-
dence of the areas of interictal and ictal activity is caused
by pediatric sample. Children have more diffuse interictal
activity and IP onset. Local accents are often absent in
the structure of the pattern due to rapid generalization of
IP [11, 12].

Conclusion

We have identified two types of IP onset in children
with FCD: generalized and local. It was shown that coin-
cidence of interictal and ictal activity are often observed
in patients with local type of IP onset. Certain correla-
tions of FCD types with features of IP onset were re-
vealed. Local type of IP onset was predominantly ob-
erved in patients with FCD type II, generalized type — in
those with FCD type I and III. Type of IP onset did not
significantly depend on localization and spread of brain
injury.

Data about IP onset may be used for preoperative ex-
amination in patients with symptomatic epilepsy in order
to suggest histological diagnosis and determine further
treatment strategy. Comparison of concordance of loca-
lization of ictal and interictal activity with surgical out-
comes is scheduled in the following trials.

Authors declare no conflict of interest.

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**Comment**

The article is devoted to the peculiarities of ictal and interictal activity in children with focal cortical dysplasia (FCD). The relevance of this issue is determined by the prevalence of cerebral cortex malformations in patients with pharmacoresistant epilepsy. The purpose of preoperative examination in these patients is localization of epileptogenic trigger area. It is believed that zone of IP onset is the closest to epileptic zone. In this regard, the key examination methods are electrophysiological studies (video-EEG-monitoring with registration of discharges and invasive monitoring if VEM is not informative). However, there is still no single standard regarding certain biologic activity as the beginning of ictal pattern. The purpose of this work is to study EEG-patterns of IP onset, their relationship with lesion of cerebral cortex, and the concordance of ictal and interictal activity in patients with FCD. The authors retrospectively analyzed 38 patients aged from 6 months to 15 years with FCD who underwent surgical treatment of pharmacoresistant epilepsy in the Burdenko Neurosurgery Center. Six variants of IP onset were identified. The authors showed that coincident zones of ictal and interictal activity are usually observed in patients with local type of IP onset. Patients with FCD type II had local onset of ictal pattern as a rule. FCDs type I and III were followed by generalized onset of ictal pattern. Diffuse activity at the beginning of IP was registered in approximately half of the patients that can indicate a tendency to the rapid spread and generalization of ictal activity. This feature is typical for these patients.

*M.V. Aleksandrov (St. Petersburg)*
Evaluation of Transsphenoidal Adenomectomy Outcomes in Acromegaly Using Different Remission Criteria

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Almazov National Medical Research Center, St. Petersburg, Russia

For a long time, surgical removal of somatotropinoma using the transsphenoidal approach has been the first stage of treatment in most acromegaly patients. For the past decades, the efficacy criteria for surgical treatment of acromegaly have significantly changed, which requires appropriate correction.

**Purpose.** We aimed to evaluate the results of transsphenoidal adenomectomy in acromegaly patients using various criteria for disease remission.

**Material and methods.** The study included patients with newly diagnosed acromegaly who underwent transnasal transsphenoidal endoscopic adenomectomy performed by a single neurosurgeon. The surgical treatment outcomes were evaluated 6 months after operative intervention based on levels of IGF-1, OGTT, and GH. The obtained data were analyzed using different threshold values for the level of GH nadir during OGTT: criteria A<2.0 ng/ml, criteria B<1.0 ng/ml, and criteria C<0.4 ng/ml to assess acromegaly remission, along with matching of the IGF-1 level to the reference range for a given gender and age.

**Results.** The study included 70 patients (52 females and 18 males) with a mean age of 52.2±11.5 years (29 to 73 years). The baseline IGF-1 level exceeded the upper limit of the reference range 3.3±1.4 (1.1―7.3)-fold, on average. The baseline mean basal GH level was 34.2±41.7 (1.2―192.0) ng/ml. The mean pituitary adenoma size was 16.7±8.6 (4.3—46.0) mm; 18 (26%) out of 70 patients had pituitary microadenoma, and 52 (74%) patients had macroadenoma. Six months after surgery, acromegaly remission met criteria A in 47 (67%) patients, criteria B in 28 (40%) patients, and criteria C in 18 (26%) patients.

**Conclusion.** Our findings demonstrate that evaluation of transsphenoidal adenomectomy outcomes in treatment of acromegaly patients depends on the criteria chosen for assessing remission. This feature should be considered when comparing outcomes of surgical treatment for acromegaly in different years. Probably, introduction of the 2010 criteria should be accompanied by revision of the previous remission indicators.

**Keywords:** neuroendocrinology, growth hormone, acromegaly, transsphenoidal adenomectomy, acromegaly remission.

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**Abbreviations:**
- GH — growth hormone
- IGF-1 — insulin-like growth factor (somatomedin)
- MRI — magnetic resonance imaging
- OGTT — oral glucose tolerance test

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Acromegaly is a neuroendocrine disease caused by autonomic increased release of growth hormone (GH). Pituitary adenoma is the most common substrate of the disease [1]. Chronic excess of GH results impaired quality of life, 2—3-fold increase of overall mortality and decreased life expectancy by 10 years on average primarily due to cardiovascular, respiratory and malignant complications [2]. Clinical and biochemical remission of acromegaly is associated with mortality rate similar to that in general population [3]. Transsphenoidal removal of GH-producing adenoma is the first stage of treatment of patients with acromegaly as a rule [4—6].

The criteria of the effectiveness of surgical treatment of acromegaly have changed significantly over the past decades. In the 1980s, the goals of treatment of acromegaly were minimal clinical manifestations of increased release of GH and its concentration less than 10.0 ng/ml [7]. Feasibility of lower levels of GH in patients with acromegaly was confirmed later [8, 9], and A. Giustina et al. defined acromegaly remission in 2000 [10]. So-called Cortina criteria were accepted at the international meeting of experts for the treatment of pituitary diseases (Cortina, Italy). A combination of the following parameters determined postoperative remission of acromegaly: no clinical signs of disease, basal level of GH less than 2.5 ng/ml, nadir GH level after an oral glucose tolerance test (OGTT) less than 1.0 ng/ml and normal values of insulin-like growth factor 1 (IGF-1). Further studies have demonstrated the need for even lower levels of GH in patients with acromegaly after surgery [3, 11, 12]. Therefore, Acromegaly Consensus Group reviewed the criteria of remission in 2005 and 2010 [13, 14]. Current recommendations (2010) determine effective surgical treatment of acromegaly in case of normal values of IGF-1 for certain sex and age, basal GH level less than 1.0 ng/ml and GH suppression less than 0.4 ng/ml in OGTT with glucose 75 g [14].

Different authors [6, 15—29] reported incidence of postoperative remission of acromegaly about 80—90% in patients with pituitary microadenomas and 40—60% in
patients with macroadenomas. However, some of these trials used different criteria of remission, which were not consistent with current clinical guidelines in some cases [17–23]. Currently, there are few studies [6, 24–27, 29] devoted to the effectiveness of surgical treatment of acromegaly, where the authors use remission criteria published in 2010. Some authors reported similar effectiveness of surgical treatment with generally accepted indicators [24–26], whereas surgical effectiveness was lower in other studies [6, 27]. Probably, incidence of postoperative remission of acromegaly depends on the selected criteria.

The purpose of this study is to evaluate the results of transsphenoidal adenomectomy in patients with acromegaly depending on different remission criteria.

Material and methods

It was a cohort retrospective observational study. There were 70 patients aged 29—73 years with a newly diagnosed acromegaly who were hospitalized in the endocrinology departments of the Almazov Research Center in 2014—2016. Exclusion criteria were age younger than 18 years and older than 75 years, previous chiasmal-sellar surgery, current intake of somatostatin analogues or dopamine agonists, previous radiotherapy.

Diagnosis of acromegaly was based on complaints, symptoms, increased IGF-1 level for certain sex and age and nadir GH level ≥1.0 ng/ml in OGTT. Pituitary adenoma was diagnosed using contrast-enhanced MRI of chiasmal-sellar area (Magnetom Trio A Tim 3.0 T, Siemens, Germany).

Serum IGF-1 was determined by a quantitative enzyme immunoassay (OCTEIA IGF-1, IDS Ltd., Boldon, United Kingdom); variation of reproducibility within series is 4.6—7.2%, between series — 4.3—6.5%. Unit of measurement is ng/ml. Reference range: 18—20 years — 141—483; 21—25 years — 116—358; 26—30 years — 117—329; 31—35 years — 115—307; 36—40 years — 109—284; 41—45 years — 101—267; 46—50 years — 94—252; 51—55 years — 87—238; 56—60 years — 81—225; 61—65 years — 75—212; 66—70 years — 69—200; 71—75 years — 64—188; 76—80 years — 59—177; 81—85 years — 55—166.

Electrochemiluminescence method (Roche Diagnostics, Mannheim, Germany) was used to determine serum GH concentration. Unit of measurement is ng/ml, reference range for men — 0.03—2.47 ng/ml, for women — 0.13—9.88 ng/ml.

A 75-gram OGTT was performed in standard fashion: baseline blood sample to determine GH level, glucose solution (75 g) intake and subsequent blood samples after 30, 60, 90 and 120 min to determine GH level.

Gadobutrol (7.5 ml) was used as MRI contrast agent (Gadovist, Bayer Pharma AG, Germany). Maximum dimension of pituitary microadenoma was <10 mm, macroadenoma — >10 mm.

All study patients underwent transnasal transsphenoidal endoscopic adenomectomy as soon as the diagnosis was confirmed. The same neurosurgeon carried out the procedures.

Table 1. Acromegaly remission criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Remission criterion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Baseline GH level &lt; 2.5 ng/ml</td>
<td>Nadir GH level in OGTT &lt; 2.0 ng/ml</td>
<td>Remission criteria used by some authors [17, 18, 21]</td>
</tr>
<tr>
<td>C Baseline GH level &lt; 2.5 ng/ml</td>
<td>Nadir GH level in OGTT &lt; 1.0 ng/ml</td>
<td>Remission criteria (2000)</td>
</tr>
<tr>
<td>C Baseline GH level &lt; 1.0 ng/ml</td>
<td>Nadir GH level in OGTT &lt; 0.4 ng/ml</td>
<td>Remission criteria (2010)</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of patients (n=70)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD, %</th>
<th>Min—max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.2±11.5</td>
<td>29—73</td>
</tr>
<tr>
<td>Duration of disease, years</td>
<td>6.0±3.0</td>
<td>2—15</td>
</tr>
<tr>
<td>GH level, ng/ml</td>
<td>34.2±41.7</td>
<td>1.2—192.0</td>
</tr>
<tr>
<td>IGF-1 in a patient/IGF-1 ULN, ng/ml</td>
<td>3.3±1.4</td>
<td>1.01—7.3</td>
</tr>
<tr>
<td>Dimension of pituitary adenoma</td>
<td>16.7±8.6</td>
<td>4.3—46.0</td>
</tr>
<tr>
<td>microadenoma</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>macroadenoma</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>extracellular growth</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

Footnote. IGF-1 — insulin-like growth factor-1; ULN — upper limit of normal.
all procedures in the neurosurgery department of the Almazov Research Center.

Surgical outcomes were analyzed in 6 months after surgery. Concentration of IGF-1 and GH (including OGTT) was determined in all patients. We have analyzed these data using various remission criteria (Table 1). Local ethics committee approved study protocol. All patients signed informed consent to participate in the study. Statistical analysis was carried out using Statistica 10.0 software package. Data are presented as mean, standard deviation (minimum and maximum).

**Results**

Characteristics of 70 study patients with a verified diagnosis of acromegaly are presented in Table 2. Mean age of patients was 52.2±11.5 years (range 29—73, duration of disease — 6.0±3.0 years (range 2—15).

Preoperative IGF-1 level was 739.8±418.5 (range 233.4—1700.7) ng/ml and exceeded upper limit of normal by 3.3±1.4 (1.1—7.3) times on the average.

Basal GH level prior to surgery ranged from 1.2 to 192.0 ng/ml (mean 34.2±41.7).

MRI of chiasmal-sellar area revealed pituitary adenoma 4.3—46.0 (16.7±8.6) mm in all study patients. Pituitary microadenoma was observed in 18 (26%) out of 70 patients, macroadenoma — in 52 (74%) patients. Extravascular growth was diagnosed in 33 (47%) patients including 1 (5%) out of 18 patients with microadenoma and 32 (62%) out of 52 patients with pituitary macroadenoma.

Remission criteria A and B of acromegaly were noted in 47 (67%) and 28 (40%) patients in 6 months after transsphenoidal adenomectomy. According to remission criteria C (2010), surgical treatment was effective in 18 (26%) out of 70 patients (Fig. 1). Patients with pituitary micro- and macroadenomas were separately analyzed. Criteria A, B and C determined effective surgical treatment in 16 (88%), 9 (50%) and 9 (50%) out of 18 patients with pituitary microadenoma, respectively. Biochemical remission of acromegaly according to criteria A, B and C was observed in 38 (73%), 19 (37%) and 9 (17%) out of 52 patients with pituitary macroadenoma, respectively (Fig. 2).

**Discussion**

We have analyzed surgical treatment of patients with acromegaly at the Almazov Research Center. Initially, we used remission criteria proposed in 2010 [14]. Overall incidence of remission in 6 months after surgery was 26%, in patients with microadenoma — 50%, in those with macroadenoma — 17%. These values significantly differed from the literature data [15, 16]. The majority of authors [6, 17–23, 28] reported incidence of acromegaly remission near 80% for microadenoma and about 50% for macroadenoma after transsphenoidal adenomectomy [7, 15, 16]. Analyzing these studies [17–23], we found higher threshold value of GH level in OGTT as a remission criterion for acromegaly after surgery in the majority of reports compared with criteria proposed in 2010. For example, in the large trial [18], overall incidence of remission was 57% including 91% of patients with pituitary microadenoma and 48% with macroadenoma. Remission criteria included normal IGF-1 level or GH level suppression below 2.0 ng/ml in 75-gram OGTT. C. B. Auregard et al. [20] reported incidence of postoperative remission of acromegaly near 52% (82% for microadenoma; 47% for macroadenoma). Remission criterion was a combination of normal IGF-1 level and GH suppression in 75-gram OGTT less than 1.0 ng/ml.
Considering these data, we evaluated surgical outcomes using different remission criteria. The criteria recommended by the endocrine community in 2000 [10] (criteria B) and the criteria used by various authors for assessment of the effectiveness of surgical treatment of acromegaly [17, 18, 21] were selected.

Criteria B determined overall incidence of remission equal to 40% including 50% of patients with microadenoma and 37% with macroadenoma. These values turned out to be more comparable with the results obtained by other researchers. P. Nomikos et al. [28] reported remission in 57.3% out of 506 patients with acromegaly after transsphenoidal adenomectomy. The authors estimated incidence of remission depending on dimension of adenoma and features of growth of macroadenoma. Patients with microadenoma and macroadenoma associated with intrasellar growth had similar incidence (75.3 and 74.2%, respectively). At the same time, this value was much lower and depended on the direction of growth in patients with extrasellar growth. Thus, suprasellar adenoma without chiasmal compression was followed by remission rate 44.5%, tumor with chiasmal compression — 33.3%, adenoma with parasellar growth and germination of cavernous sinus — 41.5% [28]. There were 47% of patients with extrasellar growth of pituitary adenoma in our study. We did not evaluate incidence of remission for each variant of extrasellar growth due to small sample size.

J. Shimon et al. [21] used criteria A in analysis of 98 patients with acromegaly. Surgical intervention was effective in 74% of patients (84% for microadenoma, 64% for macroadenoma). We obtained similar data (67% of patients with remission in the entire sample). Remission of acromegaly was achieved in 88% of patients with microadenoma and in 60% of patients with macroadenoma. Thus, incidence of remission in our study was more comparable with that in other researches if acromegaly remission criteria propose in 2010 were used.

In recent years, various trials devoted to an efficacy of transsphenoidal adenomectomy in patients with acromegaly have been published. Remission criteria proposed in 2010 were used in these reports [6, 24–27]. In 2016, D. Starnoni et al. [29] published meta-analysis of the effectiveness of surgical treatment of acromegaly based on the remission criteria adopted in 2010. Meta-analysis included 13 reports and 1105 patients. According to these data, overall incidence of remission was 54.8% including 77.9% among patients with microadenoma and 52.7% of patients with macroadenoma. Invasive pituitary macroadenoma was followed by remission rate 29%, non-invasive macroadenoma — 68.8% [29]. However, data of various studies included in this meta-analysis were discordant. Some authors used criteria proposed in 2010 and reported lower incidence of remission compared with the expected statistics [24—26]. So, F. Albarel et al. [24] analyzed 155 patients and reported overall incidence of remission 37.4% including 65% of patients with pituitary microadenoma and 31.6% of patients with macroadenoma. C. Hofstetter et al. [25] published their research in 2010 and reported overall incidence of postoperative remission of acromegaly 37.5% according to remission criteria proposed in 2010. S. Sarkar et al. [26] analyzed 113 patients with acromegaly including 52% of patients with invasive pituitary adenomas. Overall effectiveness of surgery was 31.9% (56% for microadenoma, 27.8% for macroadenoma). At the same time, some reports [6, 27, 30] demonstrated high remission rates. So, J. Jane et
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Conclusion

According to our study, the results of transsphenoidal adenomectomy in the treatment of patients with acro-
mega rely on the selected criteria for assessing re-
mis sion. This feature should be considered in analysis of the
results of surgical treatment of acromegaly. Probably,
traditional remission rates require revision after intro-
duction of the criteria in 2010. Feature of the sample cab
also influence the values: number of patients with micro-
and macroadenoma, growth of macroadenoma. The
limitations of our study are small sample size, follow-up
(6 months), no analysis of the features of macroadenoma
growth. Therefore, further follow-up and study are re-
quired.

Authors’ participation:
Concept and design of the study — U.A., E.N.
Collection and analysis of data — A.I., A.V., N.V.
Statistical analysis — A.I.
Writing text — A.I., U.A.
Editing — A.I., U.A., V.Yu., E.N.

Authors declare no conflict of interest.


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Acromegaly is a neuroendocrine disease accompanied by progressive disability of patients and reduced life expectancy. Transphenoidal removal of pituitary adenoma is currently preferred for this disease. The procedure should be performed by well-experienced neurosurgeons at large specialized medical centers. Diagnostic and especially remission criteria of acromegaly including those after adenomectomy have significantly changed over the past decades towards more “strict criteria”. Various studies have shown that acromegaly-associated mortality is similar to that in general population if GH and IGF-1 levels are completely controlled. Thus, stable hormonal control after surgery will ensure optimal quality of life.

Postoperative acromegaly remission rate was 50% in patients with microadenoma and 17% in those with pituitary macroadenoma if the criteria proposed in 2010 were applied. In case of criteria proposed in 2000, the same values were 50% and 37%.

Evaluation of surgical outcomes depends on the selected criteria for assessing remission. A comparative analysis of acromegaly remission rate in various foreign studies was performed using modern criteria. Medication and/or radiotherapy should be considered if postoperative remission of acromegaly determined by modern criteria is absent.

Surgical treatment in various neurosurgical clinics should be considered if postoperative remission of acromegaly determined by modern criteria is absent. Surgical treatment in various neurosurgical clinics should be evaluated using modern uniform criteria. In particular, this information is necessary to assess the quality of surgical treatment and to guarantee highly qualitative medical care.
Oculomotor Nerve Neurinomas. Case Reports and a Literature Review


Burdenko Neurosurgical Institute, Moscow, Russia

Oculomotor nerve neurinoma not associated with neurofibromatosis type II is an extremely rare pathology. According to the topography, cisternal, cisternocavernous, cavernous, orbitocavernous, and orbital tumor groups are distinguished. The clinical picture of the disease is characterized mainly by either oculomotor disorders or pyramidal symptoms, depending on the tumor localization. Neurinomas of the oculomotor nerve rarely occur without oculomotor disorders. However, in some patients with these tumors, the third nerve function remains intact. In this paper, we present clinical cases of two patients with oculomotor nerve neurinomas and analyze the relevant literature.

Keywords: oculomotor nerve neurinoma, schwannoma.

Material and methods

There were 2 patients with oculomotor nerve neurinomas at the Burdenko Neurosurgery Center. Their characteristics are shown in the Table. Trigeminal neurinoma was suspected in the first patient considering clinical and radiological data. There were no oculomotor disorders prior to surgery. Tumor was removed through retrosigmoid approach.

Bilateral symmetrical tumors affecting cisternal segments of both oculomotor nerves were diagnosed in the second patient. The patient refused the proposed surgery.

Case report 1

A 66-year-old patient L. had a disease manifested by generalized convulsive seizure in 2012. The patient was examined at the Burdenko Neurosurgery Center and refused the proposed surgery. There was a re-hospitalization in 2015. According to CT-data, a large right-sided tumor in the medial areas of the middle cranial fossa and in interpeduncular cistern compressing the brainstem was observed (Fig. 1). MRI was contraindicated due to implanted pacemaker. The tumor significantly increased (previous images were not preserved). Neurological examination revealed mnemonic disorders (fixation amnesia, reduced criticism), right-sided facial hypesthesia in the area supplied by trigeminal nerve, spontaneous horizontal nystagmus, cerebellar disorders. Oculomotor disturbances were absent. Trigeminal neurona was suspected considering symptoms and CT-data.

Case report 2

There were 2 patients with oculomotor nerve neurinomas at the Burdenko Neurosurgery Center. Their characteristics are shown in the Table. Trigeminal neurinoma was suspected in the first patient considering clinical and radiological data. There were no oculomotor disorders prior to surgery. Tumor was removed through retrosigmoid approach.

Bilateral symmetrical tumors affecting cisternal segments of both oculomotor nerves were diagnosed in the second patient. The patient refused the proposed surgery.

Abbreviations:
CT — computed tomography
MRI — magnetic resonance imaging
MRI-AG — magnetic resonance angiography
PET — positron emission tomography
SCT — spiral computed tomography
SCT-AG — spiral computed angiography

Neurinoma (schwannoma) of the oculomotor nerve is a typical benign tumor composed of Schwann cells. For the first time, W. Kovacs described schwannoma of the oculomotor nerve in 1927 using autopsy data [1]. Sixty-three patients with this disease have been reported since that date up to 2016. A. Huber reported the largest sample involving 3 patients [2]. Other publications are case reports as a rule.

P. Celli et al. divided oculomotor nerve tumors into three groups using the classification of trigeminal neurinomas topography by G. Jefferson: 1) cisternal (tumor composed of cisternal nerve segment); 2) cisternal-cavernous (tumor is located both in interpeduncular cistern and cavernous sinus); 3) cavernous (tumor is composed of nerve segment traversing the wall of the cavernous sinus and located in the medial areas of middle cranial fossa) [3, 4]. Orbital-cavernous and orbital groups were distinguished later [5]. Orbital-cavernous tumor is predominantly located in the orbit with a mild spread into cavernous sinus through the superior orbital fissure. Small (<10 mm), medium (11—30 mm) and large (>30 mm) neurinomas are distinguished depending on their dimension [6].

The most common symptoms of oculomotor nerve neurinoma are oculomotor disorders, ptosis, and impaired photoreaction. However, there are reports of patients without symptoms of oculomotor nerve lesion [7]. We report 2 patients with oculomotor nerve neurinoma and a literature review.

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Tumor was removed through the right-sided retrosigmoid approach on August, 10, 2015. Intraoperative examination revealed intact trigeminal nerve throughout and its tumor-induced posterior displacement. Yellow tumor of moderate density without a clear capsule was placed anteriorly. The tumor formed a large node which was located in the medial area of the middle cranial fossa and spread down up to the clivus. Wide dissection of tentorium cerebelli was followed by removal of tumor using an ultrasonic sucker. Central and lateral segments of tumor were consistently removed. Tumor surface was separated from the brain stem. Certain difficulties were noted during dissection of medial segments due to close adherence to the brain stem. Segment of the oculomotor nerve was found during mobilization of anterior pole of tumor. Further, this nerve disappeared inside the tumor. Laterally, tumor spread into dura mater duplicature (entering of oculomotor nerve into the cavernous sinus) and invaded cavernous sinus. Thus, tumor originated from cisternal segment of the right oculomotor nerve at the site of its entry into the cavernous sinus. Tumor was completely removed.

Control CT of the brain confirmed radical excision of the tumor. There were no obvious hemorrhagic or ischemic complications (Fig. 2). Paralysis of the right oculomotor nerve, left-sided hemiparesis score 1 and impaired swallowing occurred after surgery (most likely due to difficult dissection of tumor from the brain stem). Medication and rehabilitation resulted regression of swallowing disorders and improved movements in the left extremities (score 3—4), oculomotor nerve paralysis was persistent. The patient was discharged in 46 days after surgery for further rehabilitation.

A microscopic examination revealed a typical morphological pattern of neurinoma with Antoni A (dense foci of fibrillary elongated cells) and Antoni B regions (loosely arranged cells with foci of lipoidosis, angiomatosis, hyalinosis of the vessel walls and hemosiderin accumulations as signs of previous hemorrhages). Moreover, few foci of significant nuclear polymorphism were identified. Mitoses and necrotic changes were not found (Fig. 3).

**Case report 2**

A 62-year-old patient Kh. has suffered bilateral ptosis and diplopia since 2002. In 2009, outpatient examination at the Burdenko Neurosurgery Center revealed bilateral lesion of oculomotor nerves: moderate ptosis on the right (palpebral fissure up to 5 mm), almost complete ptosis on the left (palpebral fissure up to 2–3 mm), severe

---

**Characteristics of patients with oculomotor nerve neurinoma**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age, years</th>
<th>Tumor dimension</th>
<th>Localization of tumor</th>
<th>Oculomotor disorders</th>
<th>Other neurological complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F., 66</td>
<td>Large (&gt;30 mm)</td>
<td>Cisternal-cavernous (on the right)</td>
<td>No</td>
<td>Mnestic disorders. Right-sided trigeminal nerve failure. Cerebellar symptoms. Secondary brain stem disorders (nystagmus)</td>
</tr>
<tr>
<td>2</td>
<td>M., 62</td>
<td>Small (&lt;10 mm)</td>
<td>Cisternal (bilateral)</td>
<td>Bilateral oculomotor disorders</td>
<td>No</td>
</tr>
</tbody>
</table>

---

**Fig. 1. Case report 1. Contrast-enhanced CT of the brain. Axial, frontal and sagittal scans. Right-sided tumor in the medial areas of the middle cranial fossa and in interpeduncular cistern is revealed.**

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paralytic divergent strabismus, no eye movements in any direction, anisocoria (pupil of medium width without light reflex on the right, moderate mydriasis without light reflex, keratitis on the left) (Fig. 4). MRI of the brain diagnosed bilateral round-shaped tumors within the cisternal segments of both oculomotor nerves (Fig. 5). There were no clinical manifestations of Recklinghausen disease. The patient refused the proposed surgery. His fate is unknown.

Discussion and literature review

Intracranial neuromas account 7–8% of all intracranial neoplasms [3]. As a rule, these are benign tumors originating from sheaths of the vestibulocochlear and, less commonly, trigeminal nerves [8]. Schwannoma of the nerves innervating eye muscles including cranial nerve III without neurofibromatosis type II is an extremely rare disease. Schwannoma of the right and the left oculomotor nerves can occur with equal probability. There were 3 (5%) cases (including 2 children) of malignant neuroma of the oculomotor nerve among 63 patients described in the literature [9—11].

The disease occurs at different ages, there are case reports of this pathology in a 15-month-old child and in a 79-year-old patient. Mean age was 36.8 years (40 years for women and 32.2 years for men) [9, 12]. It is noteworthy that bilateral lesion was absent in all patients without neurofibromatosis type II. In our report, patient had bilateral lesion of the oculomotor nerves, but symptoms of neurofibromatosis were absent.

Neurinoma of the oculomotor nerve is characterized by slow growth, that results great duration of the disease (mean period is 29 months). Analysis of the literature (63 patients) revealed the dependence of duration of the disease and localization of the tumor. Thus, slow progression is typical for cisternal neuromas (period from initial symptoms to appeal for medical care was 71.6 months). Higher growth rate was observed in patients with cavernous (26 months), orbital (13), cisternal-cavernous (11.7) and cavernous (2.8) neurinomas.

Clinical symptoms depend on localization of tumor. Diplopia was the most common primary complaint in patients with cavernous, cisternal-cavernous, orbital-cavernous and orbital tumors. Eyelid ptosis was observed in approximately ¼ of patients with cisternal and cisternal-cavernous tumors [6, 9, 13—15]. Exophthalmos as initial symptom was characteristic in patients with orbital-cavernous and orbital neuromas [16—19]. Impaired function of cranial nerves V and VI was observed in patients with cavernous, cisternal-cavernous and orbital-cavernous tumors [8, 13, 20].

The second common complaint in patients with intracranial neuromas was headache (excluding orbital-cavernous and orbital tumors). This complaint was more frequent in patients with cisternal tumors [21, 22].

Ophthalmoplegic migraine was observed only in patients with cisternal neuromas [23—26]. These patients were characterized by long duration of disease and undulating headache accompanied by transient paresis or paralysis of the oculomotor nerve. All patients with tumor spread into the orbit had impairment of visual acuity.

Neurinomas of the oculomotor nerve rarely occur without oculomotor disturbances. There are only 4 case reports describing normal function of the oculomotor nerve [7, 27—29]. Normal function of the oculomotor nerve significantly complicates diagnosis. Intraoperative examination determined type of tumor except for one case [7]. In our first clinical observation, tumor was not associated with oculomotor disturbances and manifested like a trigeminal tumor. However, intraoperative examination found intact trigeminal nerve while oculomotor
nerve entered the tumor near cavernous sinus. So, neuroma of the oculomotor nerve was concluded. Persistent postoperative paralysis of the oculomotor nerve could also indicate lesion of this nervous structure.

Severity of neurological deficit significantly depended on tumor dimension. Patients with large tumors (over 30 mm) had oculomotor disturbances combined with other neurological symptoms. Similar clinical picture was less typical for patients with medium tumors (11—30 mm). Patients with small tumors (<10 mm) had isolated dysfunction of the oculomotor nerve as a rule or no symptoms in some cases. Tumor was accidentally detected during MRI in these patients [7, 29]. Convulsive syndrome was noted in 2 patients [6, 30].

Literature review confirmed that MRI has become the main neuroimaging method for these tumors. MR-pattern depends on the presence of cysts, necrosis and fatty elements. As a rule, solid tumors are T1-hypointense, isodense to white matter in T2-weighted images and evenly accumulate contrast. Differential diagnosis must be carried out with neuromas of the adjacent cranial nerves (IV, V, VI). Imaging with high-tech methods (CT, PET, CT-AG, MRI-AG or direct angiography) may be required considering difficult differential diagnosis.

According to the literature, surgical treatment is preferred for oculomotor nerve neuromas. However, some authors question advisability of surgery and prefer follow-up and radiotherapy. This position is explained by postoperative oculomotor disorders after excision of tumor due to iatrogenic injury of the oculomotor nerve [5, 6, 20, 21, 27, 31—34]. Simultaneous repair using autologous gastrocnemius nerve in 1 patient resulted only partial recovery of oculomotor nerve function [33]. Persistent impairment of oculomotor nerve function was observed in the majority of patients despite intact structure of the nerve. Postoperative neurological deficit was transient in patients with clear symptoms of disease (headache, pyramidal and cerebellar symptoms, dysfunction of cranial nerves II, IV, V, VI, exophthalmos, epileptic seizures) except for oculomotor nerve dysfunction [35]. Re-
covery of oculomotor nerve function was observed later only in some cases (including long-term period) [13, 17].

Dimension of residual tumor remained stable even after subtotal excision as a rule. Tumor growth de novo followed by redo surgery was described only in one case [36]. Radiotherapy alone or in combination with other methods may be also effective in patients with oculomotor nerve neurinoma. However, there are few publications confirming these data [37].

**Conclusion**

Thus, oculomotor nerve neurinoma is a predominantly benign tumor and extremely rare observed in patients without neurofibromatosis type II. The main clinical manifestation of disease is impaired function of the oculomotor nerve. However, large tumors can cause cerebral, cerebellar, pyramidal symptoms and paresis of adjacent cranial nerves. Differential diagnosis requires a comprehensive assessment of anamnesis, symptoms, neuroimaging and intraoperative data. Surgical treatment usually results long-term freedom from recurrence and regression of symptoms. However, persistent dysfunction of the oculomotor nerve is a typical postoperative complication.

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Oculomotor nerve neurinoma is a predominantly benign tumor and extremely rare observed in patients without neurofibromatosis type II. It is characterized by a slow growth rate. The main clinical manifestations are various oculomotor disorders. Severity of neurological deficit depends on localization and dimension of tumor. Headache occurs later. Few authors reported normal function of the oculomotor nerve (in 4 out of 63 patients described in the literature). MRI is the main neuroimaging method. Surgical treatment is preferred in these patients. The authors comprehensively reviewed available literature devoted to this issue. A classification of tumors depending on their localization and dimension is presented. Both case reports emphasize difficult differential diagnosis with other neuromas of cranial nerves once again. The second clinical case is interesting by bilateral lesion of oculomotor nerves in a patient without neurofibromatosis. The report is interesting for neurosurgeons.

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Comment

The report is very interesting and unique for the Russian-language neurosurgical literature. Indeed, schwannomas of the oculomotor nerve are extremely rare. I would like to start from the final part of the article and note great number of references. Moreover, references cover a significant period (from the first description of tumor in 1927 until recent years). In my opinion, the fact of postoperative brain stem ischemic stroke was missed in the first case report. Apparently, this complication was caused by injury of the branches of superior or anterior inferior cerebellar artery. It is confirmed by bulbar disorders (although tumor was located much higher than inferior cranial nerves), contralateral severe hemiparesis and prolonged hospital-stay (46 days). Again, this is just my guess, since available control images do not describe state of upper brain stem. It would be also extremely interesting to follow-up the second patient with bilateral intracisternal schwannomas who refused the proposed treatment. Authors’ opinion regarding advisability of radiotherapy in this patients is also interesting. In general, the article will be interesting for neurosurgeons engaged in surgery of extracerebral tumor.

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Cerebral aneurysms occur in 2—3% of adults. Annual risk of rupture is 1—3%. Incidence and mortality from subarachnoid hemorrhage (SAH), severity of disability in survivors remain high despite quite low annual risk of rupture [1].

Microsurgical and endovascular repair of cerebral aneurysms is still associated with a significant risk of rupture that may exceed the annual risk. Thus, there is a need to understand better the risk factors of rupture and to develop non-invasive methods of diagnosis of the aneurysms with higher risk of rupture.

The mechanisms of development, growth and rupture of cerebral aneurysms are complex. It is believed that permanent hemodynamic pressure results structural changes in cerebral artery wall and their dilatation. Thus, walls of unruptured aneurysms are characterized by intimal hyperplasia and appearance of blood clots. Tissue remodeling is typical for cerebrovascular aneurysms similar to that in healing of the damaged arterial wall. Injury of the endothelium or muscle layer results smooth muscle cells (SMC) migration to the intima. Here, contractile features of these cells are replaced by proliferation and synthesis of collagen (so-called neointimal hyperplasia) [2]. SMCs proliferation, synthesis of a new matrix and blood clots reorganization are likely to increase vascular wall resistance in the constantly degrading wall of the aneurysm. Prevention of aneurysm growth and rupture is often described as “recovery and maintenance” process. Thus, SMCs phenotype regulation is crucial for degeneration and rupture of cerebral aneurysm. Different types of aneurysms are probably characterized by common pathophysiological patterns and, therefore, should have similar molecular mechanisms [3].

MicroRNAs are small non-coding RNAs containing 18—22 nucleotides. These molecules inhibit mRNA translation at the post-transcriptional level and control genes involved into various cellular processes (inflammation, cell cycle regulation, stress response, differentiation, apoptosis and migration) [4]. MicroRNA expression in patients with cerebral aneurysms is analyzed in certain reports. However, features of cellular functions and signaling pathways are still unclear [5]. It is known that several pathological processes are involved in the development of aneurysms including immune/inflammatory response activation, formation of the extracellular matrix (ECM), dysfunction of the endothelial cells, activation of the transforming growth factor beta (TGF-β), phenotypic changes of SMCs and apoptosis [6, 7]. Analysis of microRNAs associated with cerebral aneurysms confirms the relationship between these microRNAs and above-mentioned cellular and molecular mechanisms.

**MicroRNA and development of cerebral aneurysm**

**Extracellular matrix and vascular smooth muscle cells**

Vascular SMCs are the primary cellular component of the tunica media and maintain vascular wall integrity. These cells have a contractile phenotype under normal conditions. However, inflammatory stimulation of SMCs results their transformation to secretory phenotype. Lost markers of contractility and expression of pro-inflammatory cytokines and matrix metalloproteinases (MMP) characterize secretory phenotype of SMCs [8, 9]. Endothelial dysfunction, hemodynamic stress and direct damage were identified as stimuli inducing these phenotypic changes [10]. Secretory SMCs also become migratory, that results disappearance of cells in vascular wall and weakening of the wall [11]. Development of cerebral aneurysms is determined by progressive thinning of tunica media, cell loss, unstable migration of SMCs and apoptosis [10, 12].

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T. Jiang et al. [13] identified reduced expression of 18 miRNAs in specimens of cerebral aneurysm tissue in 14 patients with ruptured aneurysms. This was found to be associated with various cellular processes regulating phenotype of vascular SMCs and preservation of ECM [14, 15]. In an in vitro study, the authors revealed that miR-1 inhibits retinoic acid-induced SMCs differentiation through negative regulation of Kruppel-like factor 4 (KLF4) [16]. MiR-133 prevents proliferation and inhibits changes in vascular SMCs phenotype by suppressing the Sp-1 transcription factor (specificity protein 1) [17].

P. Li et al. [18] found a significantly increased miR-7 expression in patients with cerebral aneurysms. MiR-7 is a negative regulator of collagen expression in dermal fibroblasts. MiR-29 was involved in the pathogenesis of cerebral aneurysms due to its role in suppressing post-transcriptional expression of ECM proteins [19, 20]. These microRNAs were identified as suppressors of genes of elastin and ECM proteins in experimental researches of the aorta in mice. Clinical studies have shown that smokers have higher plasma miR-29b levels than non-smokers [21]. Experimental studies of cerebral aneurysms in rats confirmed miR-24 overexpression [22]. TGF-β protein controls proliferation, cell differentiation in the majority of cells and is involved in the pathogenesis of various diseases including cerebrovascular diseases. Platelet-derived growth factor (PDGF) has an important role in angiogenesis. M. Chan et al. [23] reported that interaction of PDGF-BB (ligand class B of platelet growth factor) and miR-24 results reduced TGF-β expression and synthetic phenotype of vascular SMCs. There are interesting data about miR-34a as a miRNA tumor suppressor. This microRNA affects both endothelial cells and vascular SMCs through regulation of cell cycle, apoptosis and aging [24]. Multiple studies have also shown the role of miR-34a in endothelial aging and dysfunction [25]. I. Badi et al. [24] reported increased expression of miR-34a in the arteries of old mice. Increased level of miR-34a is associated with reduced SM22a level (protein supporting contractile phenotype of SMCs).

Normally, extracellular matrix maintenance depends largely on the balance between the activity of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP). Disruption of this balance results advanced destruction of matrix proteins including collagen and elastin. This process leads to vascular wall weakening and increased susceptibility to hemodynamic stress. As a result, ECM degradation has been identified as a key component in the development, progression and rupture of cerebral aneurysm. This is confirmed by Western blot and immunohistochemical analysis of cerebral aneurysm wall [26]. For example, elevated serum MMP-9 level was observed in patients with aneurysmal SAH [27]. Smoking stimulates aneurysm growth and risk of rupture through the induction of MMP-2 and MMP-9 release by macrophages [28]. Increased MMP-2 and MMP-9 levels in aneurysm wall was experimentally demonstrated in rats [29]. It was also shown that smokers have an elevated MMP level and reduced level of TIMP and elastin in the carotid arteries. TIMP-1 and TIMP-2 prevent progression of cerebral aneurysms through restriction of ECM degradation associated with MMP [26].

An importance of MMP and TIMP in the development and rupture of cerebral aneurysms may be seen in the analysis of miRNA profiles. Besides structural components of ECM, miR-29 also affects MCL-1 anti-apoptotic protein and, paradoxically, MMP-2. This makes it possible to consider this miRNA as a therapeutic target for inhibition by anti-miR-29 [19, 30]. However, miR-29 inhibition was followed by the same expression of MMP-2 in mice. Moreover, MMP-2 expression was even reduced in the in vivo research with pancreatic elastase (PPE) used for development of abdominal aortic aneurysm [19]. This is important because therapeutic application of anti-miR-29 for miR-29 inhibition is based on enhanced synthesis of ECM. However, the last one may potentially be prevented by increased expression of MMP-2. MiR-29 inhibition does not result any changes in MMP-2 expression due to MMP-2 synthesis by inflammatory cells with high expression of MMP-2 [31]. An alternative explanation could be target effect of miR-29 on the DNA methyltransferase DNMT3B which epigenetically disables MMP-2 and MMP-9 [32]. Two studies reported consistent recovery of MMP-9 by miR-29 inhibition [19]. Anti-angiogenesis properties of miR-29b through suppressing MMP-2 expression have been demonstrated in research of hepatocellular carcinoma [33]. Analysis of cardiomyocytes revealed MMP-9 gene-mediated increase of the expression of endogenous microRNAs, miR-1, miR-26a, miR-30d, miR-24, miR-29a, miR-223 and miR-181c in mice that resulted improved function of cardiomyocytes and heart [34]. H. Lee et al. [22] reported expression of similar miRNAs in the model of rat with cerebral aneurysms. The authors supposed enhanced expression of these miRNAs as a protective response aimed at correcting imbalance between MMP and TIMP in cerebral aneurysm wall and preventing further development of the aneurysm [22].

Endothelial dysfunction

Cerebrovascular aneurysms usually occur in vascular bifurcation that emphasizes the role of distorted blood flow and shear stress in abnormal vascular remodeling. It was shown that shear stress in vascular wall initiates a long-lasting inflammatory response, which is especially intense in vascular bifurcation sites [35]. Endothelium as a boundary between blood flow and vascular wall has an essential value in the response to mechanical stress. Endothelial cells process mechanical stimuli of shear stress and strain, change their physical structure and initiate
intracellular cascades followed by inflammatory response through multiple mechanoreceptors on the apical and basal cellular surfaces. Nuclear factor x-B (NF-xB) is essential in endothelial dysfunction and pro-inflammatory pathways associated with multiple vascular pathologies including atherosclerosis and cerebrovascular aneurysms. NF-xB pathway initiates some events followed by further activation of epithelial cell adhesion molecule (CAM) and expression of inflammatory cytokines including interleukin 6 (IL-6), interleukin 8 (IL-8), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [36]. These signaling molecules activate monocytes, which penetrate into subendothelial space and increase endothelial permeability [35]. There are new data confirming significant role of miRNAs in the processes underlying the normal function of endothelial cells and their dysfunction. MiR-155 modulates the formation of cytoskeleton in endothelial cells in response to shear stress [37]. It is also shown that miRNAs can affect endothelial connexins and cadherins. These are main proteins of endothelial cell membrane which maintain endothelial permeability [38].

Pathological angiogenesis is also important aspect of endothelial dysfunction and progression of cerebral aneurysms. Proliferation of vasa vasorum in cerebral aneurysm wall is a putative mechanism which is followed by inflammatory cells penetration into tunica media and their degradation in the layer of vascular SMCs [39]. P. Li et al. [18] found changed expression of some types of miRNA let-7 and miR-18a in patients with cerebral aneurysms. The authors confirmed overexpression of microRNAs in endothelial cells while exactly these cells have a certain role in endothelial angiogenesis. MiR-16 is also expressed by endothelial cells and associated with angiogenesis [18].

**Inflammatory process**

Association of vascular disease and chronic inflammation was confirmed by multiple evidences while pathological inflammatory mechanisms were identified as pathogenetic triggers of cerebral aneurysms. It was proved that pro-inflammatory pathways potentiate certain processes associated with the development of cerebral aneurysms including endothelial dysfunction, changed phenotypes of vascular SMCs, ECM degeneration and transmural migration of inflammatory cells. Similarly, important pro-inflammatory cytokines including NF-xB, tumor necrosis factor-α (TNF-α), interleukin-1β and monocyte chemoattractant protein-1 (MCP-1) were associated with aneurysms [10, 40]. It was shown that mRNA expression has an important role in immunomodulation and inflammatory response. Indirect role of miRNA in atherosclerosis and abdominal aortic aneurysms (AAA) was confirmed [41]. These data may be applicable to understand the role of miRNA in the development and progression of cerebral aneurysms.

It was observed that increased activity of miR-92a and miR-712 contributes to the development of atherosclerosis due to their role in inflammatory response and proliferation of endothelial cells [41]. Experimental inhibition of miR-342–5p in mice decreased level of pro-inflammatory cytokines, such as nitric oxide synthase 2 (NOS2), and prevented progression of atherosclerosis [42]. J. Zhang et al. [42] found that inflammation can induce endothelial cells to release microRNAs associated with angiogenesis in atherosclerotic process. The exact function of miR-181b is unclear, but systemic administration of mimic miR-181b (synthetic oligonucleotides increasing expression of the target mRNA) reduced vascular inflammation in mice [43]. It is important to note that human endothelial cells exposed to TNF-α demonstrated rapid suppression of miR-181b. Inflammation associated with diabetes mellitus and hyperlipidemia alters the function of vascular SMCs by selective inhibition of the expression of miR-10a, miR-139b, miR-206 and miR-222. This results certain vascular pathology [44]. Some authors identified miR-24 as a mediator of vascular inflammation in mice with abdominal aortic aneurysms [45].

**MiRNAs as biological markers for cerebral aneurysms**

Currently, there are no definitive methods to predict aneurysm rupture. Researchers make attempts to identify biochemical markers for prediction of development and rupture of aneurysms. Marker molecule should be reliable for detection, reproducible, measurable, highly sensitive and specific regarding certain disease. MicroRNAs are potentially significant biomarkers due to their presence in the blood in a relatively stable state [46]. Plasma and serum miRNAs are in exosomes or in combination with RNA-binding proteins or lipoprotein complexes for protection against enzymatic degradation. There are various hypotheses regarding the origin of these circulating miRNAs including assumption about cellular (active) secretion and by-products of dead cells (passive secretion) [47]. MicroRNAs withstand multiple cycles of freezing and thawing and can be reliably detected in a stable form in plasma [47]. There is evidence that mRNA expression in human plasma changes under various pathological conditions including myocardial infarction, ischemic stroke and diabetes mellitus [48, 49]. Moreover, mRNA expression is cellular, tissue and phase-specific, that allows localizing the source of mRNA and determining terms of the pathological state [50].

Currently, there are limited data regarding miRNAs as significant biological markers for identification of cerebral aneurysms and their intended rupture. Microarray analysis was used in one research to study circulating miRNAs as markers of cerebral aneurysms. The authors found 223 serum miRNAs in patients with ruptured, unruptured cerebral aneurysms and in healthy ones. There were significant differences in serum miRNA expression
in patients with aneurysm and in the control group. Patients with unruptured aneurysms had significant changes in expression of 119 miRNAs, while those with ruptured aneurysms had changes of only 23 miRNAs. Real-time PCR (qRT-PCR) showed significantly higher levels of miR-16 and miR-25 in patients with cerebral aneurysms. Logistic regression model confirmed that serum miRNA-16 and miRNA-25 may be useful biological markers for assessing the risk of cerebral aneurysms [18].

Netherlandish authors identified three specific serum circulating miRNAs (miR-183-5p, miR-200a-3p and miR-let-7b) for distinguishing patients with cerebral aneurysms and healthy ones [50].

Morphological features of the aneurysm, in particular, presence or absence of secondary domes (diverticula) on the primary dome of the aneurysm are used to assess the risk of rupture. Diverticula indicate an active process in aneurysm wall and its growth. In one of the studies, serum miRNA expression was analyzed in the control group (no aneurysms), in patients with unruptured aneurysms and no secondary domes, in those with unruptured aneurysms and secondary domes, and in patients with subarachnoid hemorrhage. The authors [51] found an increased expression of 68 miRNAs and no reduced expression of the studied miRNAs in patients with cerebral aneurysms and secondary dome. Patients with aneurysms and no secondary dome had elevated expression of 4 miRNAs and reduced expression of 9 miRNAs. Patients with SAH had an increased expression of miR-3679-5p and miR-199a-5p, reduced expression of 13 miRNAs. MiR-21, miR-22 and miR-3665 were elevated in patients with ruptured and unruptured aneurysms regardless secondary dome. Some conclusions may be determined considering these data. First, miRNA expression varies significantly in healthy people, in patients with ruptured and unruptured aneurysms. This confirms supposed usefulness of miRNAs as biological markers for the identification of cerebral aneurysms. Secondly, different serum miRNA expression in patients with aneurysms with and without secondary domes can indicate changed miRNAs profiles in various periods of development and progression of the aneurysm. Thus, cellular and molecular processes associated with development, growth and rupture of the aneurysm can occur in different periods. Further understanding of miRNA profiles will make it possible to distinguish stable aneurysms with a low risk of rupture from aneurysms with a high risk of rupture and hemorrhage.

Conclusions

Incidence of aneurysm-associated complications is still high despite significant progress in endovascular and microsurgical treatment of aneurysms. Currently, it is relatively difficult to recognize aneurysms with high risk of rupture. Reliable biological markers of cerebral aneurysms and their structural and clinical evolution are being searched. MicroRNAs is an attractive area of research due to their presence in biological fluids (particularly in plasma), cellular and tissue specific expression. Their differentiated expression has been previously established for various diseases, but data regarding pathogenesis of cerebral aneurysms are limited. Currently, there are enough data to suggest that changed serum expression of miRNA indicates cerebral aneurysm. There are certain data confirming association of miRNA expression with different phases of aneurysm development. Moreover, analysis of miRNA profiles expression suggests the relationship of these miRNAs with molecular and cellular processes of cerebral aneurysm development. Research of endothelial dysfunction pathways, changes of the phenotype of vascular SMCs and impaired inflammatory response considering expression of specific RNAs makes it possible to understand their contribution to the pathogenesis of cerebral aneurysm. Further researches are needed to understand better the relationship between miRNA profiles expression and cerebral aneurysms.

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**Comment**

Etiology, pathogenesis and biological features of cerebral arterial aneurysms (AA), especially growth mechanisms, aneurysm wall transformation and rupture have been studied for decades. Instrumental survey, macro- and microscopic examinations of AA morphology resulted in a large amount of clinical information. However, molecular-genetic mechanisms of these processes have so far remained unclear. Technologies of molecular analysis of various pathological processes became a new stage in the study of AA. In this regard, this review devoted to these issues is absolutely relevant.

Regulatory function of non-coding microRNAs as one of the directions of molecular research is reviewed. MicroRNAs are predominantly known in research of carcinogenesis. Large number of references including recent reports is analyzed in the article. Obviously, the authors understand the problem well. Cellular and tissue mechanisms of aneurysm development, correlation of aneurysm phenotype and their biological features with expression of various miRNAs in the aneurysm wall are discussed.

Of course, it is rather difficult for the clinician to perceive the information in this review. Nevertheless, the review is very interest for understanding complex processes underlying the clinical course of AA.

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