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CASE REPORTS

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Topics to be covered in our next issue:

- Chiari malformation type 1: choosing the amount of surgery
- A technology for quick recovery of patients operated on for herniated discs
- Clinical guidelines for treatment of patients with brain metastases
Hemispherectomy in the Treatment of Pediatric Symptomatic Epilepsy

Burdenko Neurosurgical Institute, Moscow, Russia

Objective. Hemispherectomy is a recognized option in the treatment of symptomatic forms of intractable focal epilepsy in patients with developmental brain malformations and some acquired hemispheric lesions. The prognosis for an outcome of the technique is important in terms of indications for surgical treatment.

Materials and Methods. We described the hemispherectomy technique and its variants and analyzed our own experience surgical management of 40 children. The most common (27 cases) brain pathology was the extended unilateral cortical dysplasia with polymicrogyria or pachygyria and consequences of perinatal stroke. Six children had Rasmussen’s encephalitis; 6 patients had hemimegalencephaly; one child with the Sturge—Weber syndrome had meningeal angiomatosis. The patients’ mean age was 3 years. Functional hemispherectomy (hemispherotomy) was used in most cases (37); 3 patients underwent anatomical hemispherectomy.

Results. At the time of discharge, seizures resolved in all patients; later, no seizure recurrence was observed in 25 out of 29 cases with the known follow-up (the median follow-up was 2.5 years), which corresponded to ILAE class 1 outcomes (86%). Serious complications developed in 2 cases; one patient died; hydrocephalus and the need for bypass surgery occurred in 2 children. These results are discussed along with the literature data; indications for hemispherectomy are provided.

Conclusions. Hemispherectomy is a reliable and effective technique for treating the symptomatic hemispheric forms of epilepsy in children. In more than 80% of patients with congenital or acquired cerebral hemispheric pathology, its deafferentation or resection leads to persistent elimination of seizures. Children with severe forms of intractable epilepsy should be promptly referred to specialized centers to address the issue whether surgical treatment is reasonable.

Keywords: symptomatic epilepsy, epilepsy surgery, hemispherectomy.

Hemispherectomy is indicated for patients with epileptic seizures caused by unilateral a lesion in cerebral hemispheres. The etiological substrate of these conditions includes various congenital developmental brain malformations with disturbed neuronal migration and organization of the cortex of one of the hemispheres (cortical dysplasias, polymicrogyria, hemimegalencephaly), some progressive pathologies (Rasmussen’s encephalitis), the Sturge—Weber syndrome, as well as gliosis and cicatricial atrophic changes resulting from perinatal stroke [1—4]. An important criterion for surgical intervention is antiepileptic drug resistance.

Hemispherectomy has a long history. Since it has been first reported back in the 1950—60s, when it meant exclusively anatomical resection of a hemisphere or hemidecortication [5, 6], the technology has evolved towards minimizing the volume of the brain being resected: from functional hemispherectomy [7], when only the temporal lobe and the posterior frontal segment of the hemisphere are dissected, to the so-called transsylvian keyhole hemispherotomy [8]. In the latter procedure, hemispheric disconnection is performed mainly due to crossing of all the efferent, afferent, and commissural pathways in its depth and the volume of the dissected brain is reduced to the medial temporal lobe complex. The reason for withholding anatomic resection was the unusual complication, hemosiderosis (persistent mild bleeding and blood sedimentation on the walls of giant cavities formed instead of the resected hemisphere [9]) and frequent death cases in the long-term period (attributed to this complication by some neurosurgeons). A number of other procedures have been described, where the brain resection and dissection approaches are used in different combinations and which differ from each other mainly by the volume of the dissected brain [10, 11].

In Russia (the USSR), the first reports of hemispherectomy were made by Yu.I. Belyaev and L.Yu. Levchenko [12]. V.P. Bersnev [13] and A.S. Shershever [14] have later also reported the experience of using it; however, hemispherectomy was forgotten for many years in our country.

Materials and Methods

Forty children with intractable epilepsy caused by lesion in one of the cerebral hemispheres were operated on. The etiology and the nature of these conditions are summarized in Table 1. Congenital (cortical dysplasia, disturbed neuronal migration) and acquired pathologies (gliosis and atrophy as a result of perinatal stroke) were predominating. Patients with Rasmussen’s encephalitis and the Sturge—Weber syndrome comprised a smaller group. Patients’ age at the time of intervention ranged between 1 and 16 years (median, 3 years); body weight ranged between 8 and 65 kg (median, 14 kg). In most cases, seizure onset was observed during infancy; seizures were accompanied by a certain degree of developmental delay in almost all children and, in some patients, also by the neurologic deficit (hemiparesis). The time between
the first manifestations of the disease and the surgery varied from 5 months to 11 years (average time, 27 months). The past medical history of every patient reported the failure to eliminate seizures using drug therapy. Clinical manifestations included various tonic and atonic asymmetric seizures, clonic and myoclonic seizures, and hypomotor dialectic seizures. Being originally focal, in many cases the seizures were accompanied by generalization and a harmful effect on the healthy hemisphere. In babies, the seizures typically presented as serial infantile spasms.

All the patients underwent MRI examination and long-term videomonitoring of the intracranial electroencephalogram (EEG) with the 10—20 electrode placement. In addition to an epileptologist’s and pediatrician’s consultations, the patients were also examined by neuropsychologists in order to assess the level of cognitive development. The diagnosis and indications for surgery were discussed at the multidisciplinary conference attended by epileptologists, radiologists, physiologists, psychologists, and surgeons.

Hemispherectomy was considered to be medically indicated if the seizures were caused by strictly unilateral hemispheric lesion or developmental brain malformation and were resistant to antiepileptic drug therapy. Prompt intervention was recommended for babies with the catastrophic course of epilepsy, with progressive epileptic encephalopathy and the risk of an uncorrectable cognitive deficit. All the aspects, including the natural course of the disease, the prospects and reserves for drug therapy, as well as the expected new postoperative neurological deficit, were discussed with parents and legal guardians and mentioned in the informed consent.

The choice of a hemispherectomy approach was dictated by the anatomic features. Anatomical hemispherectomy was preferred in 3 out of 5 patients with hemimegalencephaly and severe changes in the internal structure of the lesioned hemisphere characterized by ugly narrowing, deformation and sequestration of the lateral ventricle. Functional hemispherectomy (hemispherotomy) was performed in the remaining 37 patients: transsylvian peri-insular hemispherotomy, in 27 patients and vertical parasagittal hemispheric disconnection, in 10 patients.

### The surgical technique

**Anatomical hemispherectomy (Fig. 1)**

Patient’s position on operating table was as follows: the head end is lifted slightly; the head is turned by 90° and slightly lowered; a roll is placed under the ipsilateral shoulder. A T-shaped skin incision is made. The bone flap was formed through several holes made by a cutting device to bare the temporal, parietal, most of the frontal, and a part of the occipital regions, including the midline above the upper sagittal sinus. An incision of the dura mater is made, shaped like an X with a vertical line in the middle, with the bases of the flaps facing the upper sagittal sinus, the base of the petrous part of the temporal bone and the pterional area.

Dissection of the sylvian fissure and exclusion of the middle coronal artery (CMA) in proximal direction from its branching point is performed. Next, subpial resection of the uncus and head of the hippocampus in the temporal lobe and transection of its fimbriae in the choroidal fissure along the free margin of the tentorium and the P2-segment of the posterior cerebral artery (PCA) are performed. Dissection of the anterior portions of the interhemispheric fissure and transection of the anterior cerebral artery (ACA) are carried out proximally from the point where the callous marginal branch originates. Bridging veins running into the superior sagittal sinus are then transected; dissection of the cistern of corpus callosum and its incision between the both ACA are performed to allow penetration of the ipsilateral lateral ventricle into it. The genu of the corpus callosum and its minor forceps are transected along the A2 segment of the ACA. An incision in the wall of the vestibule of the lateral ventricle is made along the lateral margin of the optic thalamus until the roof of the temporal horn, up to its apex, with transection of the fibers of the radiate crown. The major forceps of the corpus callosum are transected and the PCA is excluded near its P3 segment, next to the free margin of the cerebellar tentorium. The parieto-occipital and then temporal hemispheric parts are lifted, with consecutive transection of veins at the base and exclusion of the temporal branches of the PCA. By this time, the hemisphere has been dehematized and is held on its place only by the frontal portion of the uncinate fascicle. It is resected in the

### Table 1. Etiology and the structural/anatomical substrate of an epileptogenic lesion

<table>
<thead>
<tr>
<th>Etiology of an epileptogenic lesion</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs.</td>
</tr>
<tr>
<td>Unilateral diffuse cortical dysplasia</td>
<td>14</td>
</tr>
<tr>
<td>Hemispheric gliosis and atrophy (consequences of perinatal stroke)</td>
<td>13</td>
</tr>
<tr>
<td>Rasmussen’s encephalitis</td>
<td>6</td>
</tr>
<tr>
<td>Hemimegalencephaly</td>
<td>6</td>
</tr>
<tr>
<td>Sturge—Weber syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>
lateral direction, starting from the foramen of Monro towards the apex of the temporal horn (at the base, along the A1 segment of the ACA and immediately anterior from the anterior perforated plate). Next, the hemisphere is removed en bloc. Before that, the olfactory nerve is transected in the anterior cranial fossa to avoid liquorrhea. The subcortical block that includes the optic thalamus and a portion of the lenticular nucleus remains in its place; the vascular plexus is coagulated along its entire length. The foramen of Monro is plugged with the muscle. The meninx is closed with the running suture and attached to the edges of the trephine opening and, in several spots, to the bone flap, which is returned to its original site and fixed with bone sutures.

The aforesaid procedure of en bloc resection was used in 2 of 3 our cases. In one child with extremely severe changes in hemispheric anatomy, we had to resect the hemisphere stepwise: first, the temporal lobe, then the frontal lobe, and eventually the parietal and occipital lobes.

Transsylvian peri-insular hemispherotomy (Figs. 2 and 3)

The procedure of transsylvian peri-insular hemispherotomy was described by us earlier [15]. This method was used in 27 patients: 9 children with polymicrogyria and diffuse hemispheric cortical dysplasia; in 10 children with consequences of perinatal stroke; in 4 patients with Rasmussen’s encephalitis; in 3 children with hemimegalencephaly; and in one child with the Sturge—Weber syndrome.

Vertical parasagittal disconnection of the hemisphere (Fig. 4)

Vertical parasagittal hemispherotomy was carried out in 10 patients: in 5 children with diffuse dysplasia of the cortex of one of the hemispheres; in 3 patients with atrophy and gliosis after perinatal stroke; and in 2 patients with Rasmussen’s encephalitis.

The surgery is carried out in patients lying supine with their head slightly elevated. A small-size craniotomy (6×3.5 cm) is performed parasagittally above the premotor-motor cortex of the lesioned hemisphere, usually using a linear skin incision. The meninges are dissected with a horseshoe-shaped incision, with its base facing the superior sagittal sinus. The cortex of the premotor region and the central gyri is dissected parasagittally for 4—5 cm. An incision in the white matter of the frontal and parietal lobes goes deep into the body of the ipsilateral lateral ventricle and its “roof” is dissected in a longitudinal direction from the anterior horn to the vestibule.

Due to this fact, most of the commissural fibers of the corpus callosum are transected. The medial wall of the vestibule is dissected, together with the hippocampal tail in the oblique transverse direction: from the chorioidal fissure towards the splenium of the corpus callosum, which is also transected through the ventricular cavity. With this maneuver, the major forceps of the corpus callosum are actually also transected (Fig. 4b, c). In order to transect the minor forceps, the genu of the corpus callosum is first penetrated from the cavity of the anterior horn towards the interhemispheric fissure. After the pericallosal artery is found, the corpus callosum is dissected subpially up- and downward, following the course of the ipsilateral ACA (Fig. 4d). In the area of the A1 segment and the anterior communicating artery, the dissection line is shifted forward, with subpial resection of the posterior sections of the straight gyrus of the homolateral frontal lobe. The ipsilateral optic nerve emerges at the wound bottom under the arachnoid sheath. Manipulations are now performed in the vestibule and body of the lateral ventricle again. Its ependyma is dissected laterally with respect to the optic thalamus; the incision is then continued deep into the white matter between the optic thalamus and the insula leading to the roof of the temporal horn, up to its apex. Subpial resection of the medial temporal complex (hippocampal head and uncus, as well as the major portion of amygdala) is usually carried out at this stage. This procedure ensures transection of fibers of the radiate crown and disconnection of the temporal lobe. The final stage of hemispheric disconnection is subpial resection of the basal portions of the frontal lobe: from the anterior horn and from the area of the posterior portions of straight gyrus in the lateral direction: towards the apex of the temporal horn (Fig. 4e). The meninx is closed with continuous suture and attached to the bone. The bone flap is fixed with bone sutures.

All the surgeries were performed under general anesthesia (fentanyl + propofol) and artificial ventilation. Preparation for a surgery included the coagulation test and timely (1.0—1.5 months before surgery) withdrawal of drugs containing valproic acid (12 patients) to reduce the risk of coagulopathy. Most children (36) required, in addition to colloid osmotic solutions, transfusion of donated blood (650 ml on average) to replace the intraoperative blood loss (up to 700 ml on average). In addition to donated blood, one child received erythrocyte suspension prepared from his own blood on a Cell Saver device. All the children were postoperatively monitored at the Intensive Care Unit for the time ranging from several hours to 17 days (median, 1 day), until extubation was performed and steady parameters of independent respiration and hemodynamics were recovered (time until extubation ranged from 1 h to 17 days; median, 5 h). All the patients underwent CT scanning of the brain within 24 h after surgery to rule out hemorrhagic complications.

Table 2 compares some parameters characterizing the two types of hemispherotomy and the short-term postoperative period for them.
Fig. 1. Anatomical hemispherectomy in a 4-year-old patient with hemimegalencephaly.

a — the typical MR presentation of right-sided hemimegalencephaly with cortical thickening, shallow and rare cerebral fissures, extensive zones of increased MR signal intensity in the white matter of the centrum semiovale (predominantly in the frontal lobe), and manifestations of pachygyria in the frontotemporal region is determined in a series of T2-weighted axial MR images. Deformation of the right lateral ventricle is also revealed; b — the appearance of the lesioned hemisphere after dissection of the dura mater (left-hand side) and the surgical wound after en bloc resection of the hemisphere (right-hand side). A good view of the falciform process and cerebellar tentorium is provided. Center: the thalamus covered with hemostatic gauze; c — the excised hemisphere (the left-hand side: the medial surface; the right-hand side: a scheme showing the dissection and resection planes: the corpus callosum is shown with white; the posterior regions of the straight gyrus of the frontal lobe and the anterior regions of the cingulate gyrus are shown with green; the subinsular white matter (the thalamus is not excised) is shown with yellow; the medial temporal complex (the amygdala, the hippocampus, and the uncus) is shown with red; d — the MR image 6 months after the surgery (T2-weighted axial and frontal MR images and the T1-weighted axial MR image are presented). A cavity filled with CSF with a subdural hygroma above it is observed at the place of the resected hemisphere; the healthy hemisphere is displaced rightwards; the proximal segment of the bypass system placed 1.5 months after the surgery is visualized (shown with an arrow).
Fig. 2. Transsylvian keyhole hemispherotomy in a 7-year-old patient with diffuse cortical dysplasia of the right cerebral hemisphere and intractable focal epilepsy (symptomatic phenocopy of the ESES syndrome). The disease debut was at the age of 3. The patient has several hundred seizures daily, mostly presenting as atypical absence seizures with palpebral myoclonia and negative myoclonus; secondary generalized seizures occur occasionally. Left-sided hemi-paresis, muscle atrophy, and underdevelopment of the left extremities. Psychoverbal development delay.

a — T2-weighted preoperative MRI. Pronounced structural changes in the cortex of the frontal, parietal, and temporal lobes of the right hemisphere, as well as its thickening and virtually complete absence of sulci are visualized; b — surgical stages: left-hand side — exposure of the sylvian fissure and the opercular cortex of the temporal, frontal, and parietal lobes; right-hand side — appearance of the surgical wound after hemispherotomy was completed. The opercular cortex is separated by spatulas; on its floor, the insula with traces of resection of its cortex is visualized. The mobilized and preserved M3 branches of the MCA are seen. in the gaps between them and the opercular cortex, along the circular sulcus of insula, there are the dissected walls of the lateral ventricle (shown with arrows); c — MRI 6 months after the surgery, a series of T2-weighted MR scans. An extensive defect of medullary substance is visualized in the right frontal-temporal region; partial resection of the right half of the corpus callosum. Compensatory expansion of the inferior horn of the right lateral ventricle is observed.
Fig. 3. Dynamics of bioelectric activity of the brain after hemispherotomy.
Top image — intracranial EEG before surgery. Long-lasting generalized bilateral epileptiform activity can be seen. Bottom image — intracranial EEG 6 months after surgery. No epileptiform activity is detected in the right and left hemispheres. Interhemispheric asymmetry is observed due to reduction of high-frequency oscillations and predominance of pathological slow-wave activity in the right hemisphere.

Results

10 days following the surgery

Seizures stopped in all the patients. Anemia was observed in 11 patients, but only four of them needed repeated blood transfusion. Nonbacterial meningitis and a two- to threefold pleocytosis in CSF were observed in 16 children. Two patients, in addition to the expected hemiplegia, presented with transient pseudobulbar palsy and dysphagia. In all the cases, wounds were allowed to heal by primary intention. All children, except to the one who died, were discharged 6—22 days after surgery (median value, 9 days).

One 6-year-old patient with hemimegalencephaly died after an attempt of performing transsylvian hemispherectomy as a result of the injury to the perforating branches of the ACA and bleeding. Death was pronounced on day 5 after surgery; ischemia and cerebral edema were the reasons.

Long-term outcomes

Bone flap osteomyelitis developed in one patient 6 months after anatomical hemispherectomy. The bone
Fig. 4. Vertical parasagittal hemispherotomy in a 5-year-old female patient with intractable symptomatic epilepsy manifesting as steadily progressive left-sided hemiclonias and hemiparesis caused by Rasmussen’s encephalitis.

a — preoperative MRI, a series of frontal T2-weighted images. Cortical atrophy in the right hemisphere is visualized, being more pronounced in the precentral and frontal regions. Blurring of the boundary between gray and white matter; regions with increased MR intensity in the subcortical and periventricular white matter on the right side; hypotrophy of the head of the caudate and an asymmetrical increase in the left lateral ventricle and total broadening of the ventricular system of the brain; b, c, d — separate surgical stages: b — transection of the hippocampal tail (shown with an arrow) at the end of the choroidal fissure (the vascular plexus is shown with an asterisk) next to the vestibule of right lateral ventricle; c — appearance of the vestibule and its medial walls. The transection line is continued to the major forceps and the splenium of the corpus callosum (under the branches of the bipolar forceps). The intact arachnoid meninges of the cistern of lateral cerebral fossa is clearly seen (the vascular plexus is shown with an asterisk); d — view into the anterior horn of right lateral ventricle. Transection of the anterior forceps, rostrum, and genu of the corpus callosum along the pericallosal artery, which is seen behind the intact cranial pia mater and arachnoid meninges between the bipolar forceps and the end of a suction device; e — MR image 3 months after the surgery; a series of T2-weighted frontal MR images. Dissection planes of the hemisphere are clearly seen against the background of a subdural hygroma and the compressed hemisphere.

flap was removed. The child is currently getting ready for cranioplasty.

Hydrocephalus with signs of increased intracranial pressure was observed in 2 (5%) patients 1.5 and 7 months after surgery. Ventriculoperitoneal shunts were placed in both patients: in the first patient with hemimegalencephaly, into the giant subdural cavity at the place of the resected hemisphere (Fig. 1) and in the second patient with consequences of perinatal stroke, into the porencephalic cavity at the place of the destroyed anterior horn of the lateral ventricle.

Twenty nine (75%) patients were followed up for 3 months to 7 years (median follow-up period, 32 months) (Table 3). In four cases, seizure relapse occurred during the first year after surgical intervention (ILAE class 3 and 4), although the seizures were less frequent than previously [16]. In the remaining 25 (86%) patients seizures stopped since the day of surgery and were no more observed. In all these cases, administration of
anticonvulsants was stopped within the first 6 months after surgery.

Table 4 lists the follow-up data depending on etiology and an epileptogenic lesion.

It should be mentioned that the hemispherotomy technique has affected the treatment outcomes. Seizures either were not eliminated or returned in 3 (50%) of the six children who had undergone vertical parasagittal hemispherotomy, while only one case was observed among the 20 followed-up cases of transsylvian peri-insular hemispherotomy.

In seven cases, after the expected aggravation of the existing hemiparesis, the muscular strength in extremities subsequently increased. Although having hobbling gait, most children became able to walk independently and use their arm when playing or gesticulating and in daily living. In other children, due to the fact that the function had already been transferred to the healthy hemisphere, the surgery had virtually no effect on motor activity or muscular strength. Nevertheless, we would like to mention that none of the patients, even after systematic rehabilitation, restored fine motor skills in the paretic hand (especially abduction and thumb kinematics). Some children continue motor and cognitive rehabilitation in different centers and home-based individual training. The fundamental turn to the better in the overall situation in patients’ families is an important outcome of treatment.

Table 2. Comparative characteristics of vertical and transsylvian hemispherotomy

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration, h</th>
<th>Blood loss, ml</th>
<th>Blood transfusion, ml</th>
<th>Duration of intensive care, days</th>
<th>CSF pleocytosis, number of patients</th>
<th>Postoperative period, patient days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical (n=10)</td>
<td>6</td>
<td>500</td>
<td>615</td>
<td>1</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Transsylvian (n=27)</td>
<td>8</td>
<td>900</td>
<td>670</td>
<td>1</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 3. The long-term outcomes of hemispherectomy

The outcome of epilepsy treatment according to the ILAE classification

Table 4. Effectiveness of surgeries vs etiology of epileptogenic lesions

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of patients (followed up)</th>
<th>Number of patients (ILAE class 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs.</td>
<td>%</td>
</tr>
<tr>
<td>Acquired</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Congenital</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Progressive</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Discussion

The resulting data are consistent with and even surpass the results of meta-analysis of 29 studies that were published in different years, up to 2013, and summarized the outcomes of hemispherectomy in 1161 patients [17]. The review indicates that stable elimination of seizures was achieved in 73.4% of all cases (in 76% out of 406 patients who had undergone hemispherotomy only, and in 80% out of 61 patients who had undergone anatomical hemispherectomy). In our series, this effect was achieved in 86% of all cases; the effectiveness of anatomical hemispherectomy was 100%, while that of hemispherotomy was 84.6%.

A similar relationship, although being less explicit than that in the aforementioned review, is seen when comparing the treatment outcomes among our patients depending on etiology and nature of epileptogenic lesion: the patients with congenital pathologies (cortical dysplasia, polymicrogyria) have a somewhat worse prognosis than those with the acquired and progressive forms (Table 4).

When discussing patients, seizure symptomatology, EEG and MRI data, we always did our best to make sure that the brain was affected unilaterally. Nevertheless, we should admit that for the situation with brain developmental malformations, the pathological changes may be more extensive and involve both hemispheres.
These independent epileptic foci that have been recognized neither by MRI nor electroclinically and are disguised by the more evident and severe pathology in the lesioned hemisphere may cause seizure recurrence.

Another reason for seizure recurrence that is more evident is that resection (disconnection) could be incomplete [17—20]. Patients who had been reoperated because of the persistent seizures were reported in some series; the outcome of reoperations was favorable [21]. The role of the insular cortex in epileptogenesis has also been discussed [22]. The base of the frontal lobe is a typical zone where some conduction pathways remain intact. This fact may accompany both variants of hemispherotomy — both transsylvian and the vertical parasagittal — and to some extent is attributed to the surgeon being over-careful at the stage of transecting the base of the frontal lobe for fear of damaging the perforating branches of the ACA and hypothalamus in a deep and narrow wound.

Another reason for seizure recurrence may be the incomplete transection of the splenium of the corpus callosum. During vertical hemispherotomy, unlike the transsylvian variant, the splenium of the corpus callosum needs to be found without imaging the free margin of the cerebellar tentorium and the falciiform process (Fig. 4c). This may mislead the surgeon and give a false impression that all the fibers comprising the major forceps of the corpus callosum and its splenium have been transected. Control CT scanning of the brain gave grounds for suspecting this situation to have happened in two of our observations with seizure recurrence after vertical parasagittal hemispherotomy.

Nevertheless, when comparing the two hemispherotomy methods in general, vertical parasagittal surgery seems to be a more preferred procedure. It takes less time, is accompanied by smaller amount of bleeding, better tolerated by patients tolerate, and is characterized by shorter length of stay. This fact has been confirmed both by our own data (Table 2) and by the literature data [23—25]. We believe that as we gain more experience, the effectiveness of vertical hemispherotomy in our series will reach the value reported in the literature data (90%) [24]. The opinion about the personalized approach when choosing a certain surgical procedure, both with allowance for patient’s clinical and anatomical features and surgeon’s preferences, is true indeed. The best method is the one that the surgeon has mastered to the greatest extent.

There have recently been many debates on the question regarding the role of insular cortex in epileptogenesis, especially in cases with seizure recurrence after temporal lobectomy. In this connection, a number of surgeons [22] deem it reasonable to combine hemispheric deafferentation and insula resection when performing the lateral variants of hemispherotomy. We employed this approach only in some children with Rasmussen’s encephalitis and polymicrogyria, according to the recommendations given by J. Schramm [8], but not in all the cases (Fig. 2b).

Active hydrocephalus requiring bypassing was reported in all the series where hemispherectomy is used. According to the literature data [17, 26—28], the rate of this complication is on average as high as 14% and varies from 8% for hemispherotomy to 30% for anatomical resections. Among our patients, this complication developed in 2 (5%) cases: in one patient, after the anatomical hemispherectomy in a child with hemimegalencephaly (Fig. 1d); in another patient, after hemispherotomy in a baby with post-stroke gliosis and a porencephalic cyst. The probability of hydrocephalus is considered to be dependent on the volume of the resected portion of the brain and reoperations [28]. It is fair to assume that the reason for death in some patients in the long-term period after anatomical hemispherectomy in a series of cases reported in the 1950—60ss [30] was not only hemosiderosis [7, 9, 29], but also the slowly but steadily progressive non-resorptive hydrocephalus. With the modern neuroimaging facilities and their accessibility, timely detection and correction of hydrocephalus make this complication a solvable problem instead of the fatal disease.

Almost at all the stages, hemispherotomy is performed deep inside the hemisphere, through the lumen of the lateral ventricle. If it is narrowed and deformed (which is observed rather frequently in children with hemimegalencephaly), navigation in the wound becomes extremely difficult. In cases like this, it is better to perform anatomical resection of the hemisphere.

Up to half of the patients in all the series with hemispherectomy are infants and children up to 2 years old; they comprised over 1/3 of our patients. It should be emphasized that these children are underweight (the median body weight among our 14 patients younger than 2 years was 12 kg); the calculated circulating blood volume (CBV) being no more than 500—600 ml. Therefore, it should be clear what a great the role anesthetists and the entire infrastructure of anesthesia and intensive care before and after surgery play in compensation for blood loss (among our patients, up to 1 calculated CBV and higher). We have encountered in literature the description of a rather high-risk approach: vascular embolization in the affected hemisphere before its resection in a child with hemimegalencephaly [31]. Surprisingly, not only did the patient survived and tolerated the procedure well but also he did not have any seizures within the entire year after the embolization. Hemispherectomy was carried out later, only because of seizure recurrence; the outcome of the intervention was rather favorable.

We are grateful to the staff of the Rehabilitation Department of the Research Center for Pediatric Health, as well as the psychologists and the teaching staff of the Center of Psychological, Medical, and Social Support at Moscow City University of Psychology.
and Education for their involvement in postoperative rehabilitation of some of our patients. Locomotor training and cognitive rehabilitation are the key components in the set of measures for helping children and their parents after hemispherectomy, which needs to be started as early as possible, before the natural mechanisms of brain plasticity are not depleted and the lost functions still can be transferred to the remaining hemisphere [32—34].

Conclusions

Hemispherectomy is a reliable and effective method for treating symptomatic hemispheric forms of epilepsy in children. In over 80% of patients with congenital and acquired pathologies affecting one of the cerebral hemispheres, their deafferentation or resection results in stable elimination of seizures. Anatomical resection of a hemisphere is a more challenging procedure than its deafferentation and is associated with the risk of hydrocephalus development in 20—30% of cases. In this connection, hemispherotomy is preferred in cases when patients have a sufficiently spacious lateral ventricle with more or less normal anatomy. Anatomical resection is reasonable in children with the abnormal structure of the ventricle and excessive weight of the medullary substance (hemimegalencephaly). The prognosis of stable elimination of seizures depends on etiology of an epileptogenic lesion. In children with acquired and progressive pathologies (hemiatrophy, post-stroke gliosis, Rasmussen’s encephalitis), the chance of success is higher than in children with congenital developmental malformations such as polymicrogyria, cortical dysplasia, and hemimegalencephaly.

Authors declare no conflict of interest.

REFERENCES


PROBLEMS OF NEUROSURGERY NAMED AFTER N. N. BURDENKO 3, 2016
The study by A.G. Melikyan et al. is based on the analysis of the vast authors’ own experience of hemispherectomy in 40 pediatric patients and is undoubtedly the largest and the most reliable series of case reports presented in Russian literature.

Hemispherectomy that was introduced by W. Dandy in 1928 and was first used to treat epilepsy by K. McKenzie in 1938, has undergone a series of significant modification. While previously being an extremely dangerous surgery associated with a high risk of injury and being used mainly in neuro-oncology, now it is a sophisticated functional procedure used in most of epileptological centers. The reason for this evolution of the surgical procedure lies in the pursuit of avoiding extensive resection of the brain tissue, which is associated with a large number of complications, and maintaining the long-lasting anticonvulsant effect.

The epileptogenic structural changes in the cerebral hemispheres that often induce catastrophic convulsant syndromes in children result in a significant neurologic deficit, intractable epilepsy, and in almost all cases, severe psychomotor development delay. Surgical treatment in childhood provides the most favorable outcome: it eliminates epilepsy and improves child’s psychomotor development. Delayed surgical intervention at adolescence eliminates seizures, while giving no hope for improvement of cognitive functions.

The article contains a detailed and comprehensive description of the surgical procedures of anatomical functional hemispherectomy (hemispherotomy) and its two variants. Its main idea is to provide a differential approach to choosing an intervention technique depending on the type of hemispheric lesion; the lesions were divided into the acquired (11 patients), congenital (12) and progressive (6) ones. The demonstrated outcomes of surgical treatment selected depending on the type of epileptogenic lesion also confirm the need to thoroughly assess the correlation between the anatomical changes in the lesioned hemisphere and the data of neurophysiological studies, especially regarding such congenital anomalies as developmental malformations caused by the abnormal migration or abnormal cortical organization.

Seizure recurrence in 3 patients diagnosed with congenital developmental anomalies once again emphasizes the bitter fact mentioned by the authors that there may be multiple anomalies in the ipsilateral hemisphere, especially the MR-negative or electroencephalographically subdominant ones, which can be the reason for the incomplete outcome of a surgery.

The success of hemispherotomy, as well as the entire surgery of epilepsy, largely depends on proper selection of patients. The authors took many factors into account, such as seizure type and localization, the intractable nature of epilepsy, the etiological aspects, the radiological and neurologic manifestations. The outcome of hemispherotomy may differ depending on combination of the aforementioned factors.

The authors have emphasized in the section reporting the comparative effectiveness of hemispherotomy variants, the vertical parasagittal option in 10 patients and transsylvian perinsular option in 27 patients, that the best outcomes were achieved using transsylvian peri-insular disconnection.

In patients with pronounced hemiparesis (hemiplegia), the negative aspect of hemispherotomy presenting as aggravation of neurologic deficit is minimal; hence, a pediatric patient and his/her parents agree to undergo this type of surgery more often. However, for the patients with the preserved neurologic status, hemispherotomy is preceded by multiple discussions with thorough analysis of the expected elimination of seizures, preservation of cognitive functions, and the inevitable aggravation of neurologic deficit. In the series of cases reported, the postoperative aggravation of hemiparesis gave way to improvement without the recovery of fine motor skills in 7 patients; in other patients, the aggravation of neurologic functions was stopped. However, some specification is needed here, since the initial neurologic status is unclear: either all the remaining patients had hemiplegia at the time of surgery or the ipsilateral hemisphere in most patients became responsible for
all the motor functions before the surgical intervention (the authors share the latter viewpoint). We believe that in order to reliably localize the motor functions, it is reasonable to use functional MRI, MRI tractography, transcranial magnetic stimulation, or even the amytal test in the preoperative examination protocol in order to determine the outcome of hemiparesis aggravation.

The presented analysis of the cases of incomplete elimination of seizures (incomplete dissection of the major forceps of the corpus callosum and the splenium upon vertical parasagittal hemispherotomy in two of these cases) emphasizes the need for choosing the more radical strategy among patients with large developmental hemispheric anomalies and significant disturbance of the normal hemispheric anatomy and structure of the ventricular system in the brain.

The detailed analysis of the literature focused on various aspects of hemispherectomy, compared to the authors’ own data on treatment outcomes, are undoubtedly indicative of the excellent surgical skills of the authors of this article and the meticulous preoperative selection of patients. The findings demonstrate that hemispherotomy allows one to reduce the volume of resection of cortical structures, to reduce the duration of the procedure and the number of complications, to reduce the blood loss volume and to reach the persistent effect of elimination of epileptic seizures.

The relatively low complication rate reported in this study, the detailed description and critical analysis of these complications leaves a feeling of a mixture of irreality and admiration because of understanding both of the extreme technical complication of the surgical intervention and the psychologically challenging and ambiguous decision making process about performing hemispherotomy and the subsequent, very important stages of treatment and rehabilitation in pediatric patients. The authors also address the questions of functional plasticity of the pediatric brain and rehabilitation in patients with the programmed aggravation of the initial neurologic status after hemispherectomy (hemispherotony), which are extremely important in the holistic approach to the treatment of such serious diseases.

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Bilateral Radiofrequency Anterior Thalamotomy in Intractable Epilepsy Patients

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Background. Identification of the crucial role of the anterior thalamic nuclei (ATN) in the generalization of seizures led to increased interest in surgical interventions in this particular area in intractable epilepsy patients. Simulation of ATN destruction in animals demonstrated its high efficacy for both preventing the seizure development and reducing the seizure rate. However, bilateral radiofrequency destruction of the anterior thalamic nuclei in humans has not been described yet.

Objective. The study objective was to perform bilateral radiofrequency anterior thalamotomy in intractable epilepsy patients and evaluate its results.

Material and methods. We performed for the first time bilateral stereotactic radiofrequency thermocoagulation of ATN in 13 patients with long-term intractable epilepsy. Before surgery, we assessed the disease duration, age of seizure onset, localization of pathological activity sources, types of seizures, morphological damages, and ongoing pharmacotherapy. All interventions were performed under local anesthesia and accompanied by intraoperative microelectrode monitoring of the neuronal activity and EEG.

Results. Seven males and 6 females, aged 22 to 48 years, were operated on. All patients had epileptogenic foci in the frontal and/or temporal lobes. MRI revealed epileptogenic structural abnormalities in 3 patients. There were no postoperative complications. According to postoperative examination, 5 patients were seizure-free; a 50% and 70% decrease in the seizure rate was noticed in 1 and 6 patients, respectively; 1 patient had no response to the surgery. The resulting effect was manifested not only in a reduction in the frequency and severity of seizures but also in a decrease in the doses of administered anticonvulsants. EEG also showed a significant improvement in the majority of patients.

Conclusion. Our experience demonstrates that bilateral radiofrequency anterior thalamotomy is a safe and effective technique to control seizures in humans. Further research will clarify, based on the clinical and EEG data, the patient selection criteria for surgical treatment.

Keywords: epilepsy, anterior thalamic nucleus, anterior thalamotomy, microelectrode analysis.

Anterior thalamic nuclei (ATN) are the anatomical and functional center of the complex of interacting cortical and subcortical structures. Most ANT connections are presented in the cortex of the frontal lobes, cingulate gyri and hippocampus [1]. The main efferent signals come to ATN from the cortex area located behind the splenium of the corpus callosum (retrosplenial cortex), the base of the hippocampus (subiculum) and mamillary bodies [2]. These connections pathogenetically determine the use of the anterior thalamic nuclei as a target for surgery in epilepsy patients with localization of the pathological activity source in the frontal and temporal lobes of the brain. Stimulation of ANT has been recently widely used due to its proven effectiveness including multifocal forms of epilepsy and forms with primary generalized seizures [3, 4].

Animal studies have shown that not only stimulation, but also bilateral destruction of the anterior thalamic nuclei allow prevention of the development of pilocarpine-induced seizures. Moreover, convulsions did not develop at all after pilocarpine administration in rats subjected to anterior thalamotomy, while bilateral stimulation of ATN in rats only allowed increase of the drug effect, i.e. the time from dosing to seizure development [5].

The study of anticonvulsant effect of bilateral degradation of ATN in humans has not been performed previously. The paper presents for the first time the description of the technique and results of bilateral radiofrequency anterior thalamotomy in intractable epilepsy patients.

Material and methods

A total of 13 adult patients (7 men and 6 women), aged from 22 to 48 years (mean age 34.5 years) were operated on. The age of disease onset ranged from 11 months to 34 years (mean age 14.8 years), disease duration ranged from 4 to 34 years (mean duration 20.9 years). Before surgery, all patients underwent magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG): video monitoring. EEG was performed using computer electroencephalograph Cadwell with recording on 19 channels in unipolar lead with separate ear electrodes.

MRI with intravenous contrast was performed according to the protocol that allows visualization of the subthalamic nuclei, red nuclei and substantia nigra for subsequent planning of stereotactic destruction as well as exclusion or confirmation of the presence of acquired epileptogenic lesions. The selection of a stereotactic target (anterior regions of the anterior thalamic nucleus, ATN) was carried out on a day preceding surgery according to the MRI data using Radionics planning system and stereotactic atlas Schaltenbrand and Wahren.

On the day of surgery, the ring of CRW stereotactic frame was fixed on the patient’s head under local...
anesthesia, and computed tomography (CT) of the brain using X-ray contrast localizer was performed. The obtained images were combined with the surgery plan using planning system, and the point of entry and electrode placement trajectory were finally determined taking into account the individual anatomy of vessels and ventricular system of the brain.

Burr holes for microelectrode analysis and subsequent thalamotomy were made symmetrically at a distance of about 3.0—3.5 cm posterior to the coronary suture while selecting the trajectory angle that provides optimum location of an electrode for radiofrequency destruction within the longest ANT anterior segment in the sagittal plane.

Intraoperative registration of neuronal activity and determination of neurophysiological boundaries of ANT were performed using Alpha Omega system for microelectrode analysis. Microelectrode for registration was placed 10 mm above the target and moved step by step for 1 mm before the appearance of neuronal signal corresponding to the anterior thalamic nucleus. After passage of the lateral ventricles and appearance of the signal, electrode immersion interval was reduced to 0.05 mm, and evaluation of the characteristics of the signal before its disappearance in the intralaminar region and appearance of the signal of the dorsomedial nucleus of the thalamus was conducted with the assessment of electrophysiological boundaries of ATN. Microelectrode was removed, and electrode for radiofrequency destruction of 1.1 mm in diameter was adjusted (diameter of the insulated portion of the electrode: 1.24 mm, length of the active tip: 3 mm) 1 mm above the lower border of the nucleus. Destruction was performed using G4 Radionics radiofrequency generator with a frequency of 480 kHz at 70 °C for 70 sec. Further, an electrode for destruction was moved 0.5 mm above the area of the first destruction using microdrive, and the second destruction was conducted with the same parameters.

Microelectrode analysis and destruction were carried out in parallel with the recording of scalp electroencephalogram. Cup electrodes were fixed according to the standard 10—20 system, registration and analysis were performed in monopolar mode with separate ear electrodes or bipolar diagonal/bipolar with a large interelectrode distance.

Monitoring of the brain activity was performed postoperatively on day 6—7 after surgery and then after 3, 6 and 12 months.

After anterior thalamotomy, all patients underwent control MRI, the obtained data were further combined on a working station with the planned trajectory and estimation of location and size of destruction foci.

Evaluation of the results of surgical treatment was conducted according to the Engel scale, ILAE outcome scale, based on the diary of seizures and control EEG at discharge and 3, 6 and 12 months after surgery.

**Results**

According to the clinical and medical history data, the results of EEG video monitoring and MRI, 9 patients had multifocal form of epilepsy without abnormalities according to MRI, 1 patient had post-traumatic epilepsy, 2 patients were diagnosed with symptomatic epilepsy associated with focal cortical dysplasia (FCD), and 1 patient had symptomatic epilepsy associated with perinatal brain damage. Clinically, all patients had multiple secondary generalized seizures with a frequency of 1 to 300 per month. In 2 patients, in addition to the secondary generalized seizures, simple partial seizures with a frequency of 2 to 100 per month were observed.

Before surgery, only 4 patients received monotherapy with the change in anticonvulsants, 9 patients received simultaneously 3 to 5 drugs.

According to brain MRI data, multiple FCD in the left frontal, temporal and insular lobes was found in 1 patient, and another patient had transmantle FCD of the right parietal lobe that were not amenable to surgical resection in both patients due to the high risk of severe neurological deficit development. MRI revealed the area of cystic glial changes in the left frontal and temporal lobes of the brain in a patient with perinatal lesion of the central nervous system as a result of hypoxia during labor. There were no morphological changes revealed in a patient with post-traumatic epilepsy by tomography brain examination.

Analysis of the general trends of bioelectrical activity of the brain prior to thalamotomy showed a reduction in the frequency and amplitude of biopotentials against the background of pronounced interhemispheric asymmetry of the rhythm frequency (1 Hz or more). A displacement of the alpha rhythm in the anterior temporal lobes was often noted.

All patients had an excessive manifestation of slow wave seizures, the diffuse ongoing nature of activity was noted in 3 cases. Zonal predominance of slow activity was registered in the frontal, central, middle temporal lobes in a form of bilaterally synchronous bursts of theta waves (Fig. 1).

Local slowing of the rhythm in 3 patients was coincided with the morphological changes of the brain substance identified by MRI. Beta rhythms, often desynchronized, were presented by the components with different frequency and usually had low amplitude. The diffuse presence of beta waves was observed more frequently in patients receiving polytherapy, especially in combination with benzodiazepines. There were no cases of high-amplitude beta activity registered.

Epileptic activity was presented by polyfocal discharges of sharp—slow wave and semi-peak—wave type (Fig. 3a). In case of deep localization of lesion, pathological activity was registered in the number of leads. The deeper the lesion was located, the greater the degree of activity generalization was observed.

Photo-
paroxysmal response was registered in 3 patients, a provocative response to hyperventilation was noted in 1 case.

Calculated commissural coordinates of the targets (ANT) are shown in Table 1.

Average vertical coordinates were about 2 mm smaller than coordinates we used for neurostimulator implantation, since, after microelectrode analysis and evaluation of neurophysiological boundaries of the nucleus, destruction was to be conducted 1 mm above the lower border of the nucleus with regard to the assumed size of the destruction zone of about 4—5 mm in diameter.

A signal of 26 trajectories (one signal on each side) was recorded intraoperatively using microelectrode analysis, a steady signal from the anterior thalamic nuclei was obtained from 23 trajectories. The signal typical for ANT was not obtained on both sides in 1 patient and on one side in 1 case. The average length of the anterior ANT segment determined by the presence of the typical signal of neuronal activity was 3.29 mm (1.9 to 5.5 mm) on the left side and 3.02 mm (from 0.7 to 4.6 mm) on the right side.

Intraoperative registration of EEG in 2 cases showed an increase in beta activity in the anteroposterior regions of the brain at the time of the passage of the electrode for microelectrode analysis in ANT and during radiofrequency thermal destruction.

According to postoperative MRI data, destruction sites were located within ATN on both sides in 12 patients, the average diameter of the destruction site was 4.1 mm (range 5.2 to 3.8 mm). In 1 patient, the destruction focus was visualized only on one side during control examination, which required the second one-sided intervention on the next day. Subsequent MRI study confirmed symmetrical location of destruction sites in the anterior thalamic nuclei in all patients (Fig. 2).

Postoperative period was uneventful in all patients. The average length of hospital stay was 11 days (range 6 to 16 days). Side effects, as well as significant changes in cognitive functions, emotional and volitional area were not observed after destruction. Patients did not show complaints of impaired memory and attention.

At the time of discharge, EEG showed improvement of frequency-spatial characteristics of the basic rate, increased alpha rhythm to 9—10 oscillations per second and increased amplitude of the complexes in the parietal-occipital leads to 70 µV in 3 patients (Fig. 3b).

In other cases, the frequency spatial distribution and distribution of epileptic discharges remained unchanged. In the early postoperative period, a significant decrease

Fig. 1. Fragments of epileptic activity recordings by EEG of the patient prior to radiofrequency anterior thalamotomy (explanation is in the text).
in the number of attacks (50 to 90%), as well as change in their nature and duration was observed in 10 patients out of 13. Phototest resistance occurred in two patients with previously registered photo paroxysmal response. In one case, epileptic activity was not registered by EEG 12 months after the procedure.

All patients in the early postoperative days had correction of anticonvulsant therapy performed in accordance with the type of seizures and individual tolerability: 4 patients were converted to monotherapy, 9 patients were converted to combination of two drugs at average therapeutic doses.

Efficiency of anterior nucleus thalamotomy 3 and 6 months after surgery is presented in Table 2.

Evaluation of the results of surgical treatment by the existing standard scales in the period of 6 and 12 months after surgery is available for 5 patients. A complete absence of seizures was noted in 3 patients out of them 6 months after destruction, sparse secondary generalized seizures were observed in 1 case, and 1 case showed a significant improvement with the preservation of rare partial seizures. Two out of the 3 patients, the follow-up duration for whom is 5 months, note the complete absence of seizures.

**Discussion**

The anterior thalamic nuclei directly associated with mamillary bodies through mammillothalamic tract are also closely associated with other structures of the limbic system, which play an important role in maintaining the mechanisms of emotional tone and different types of memory and attention. Through its afferent and efferent connections, ATN affect the major limbic structures, including the entorhinal cortex and the hippocampus.

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**Fig. 2.** Magnetic resonance tomography scans of the patient after radiofrequency anterior thalamotomy on the sagittal (a) and coronal (b) sections. Destruction zones are visualized within ANT.

**Fig. 3.** Fragments of epileptic activity recording by EEG of the patient a month after radiofrequency anterior thalamotomy (explanation is in the text).
These anatomical and functional relationships allow one to consider this group of nuclei as the most reasonable target in the surgical treatment of patients with intractable epilepsy in the presence of foci of pathological activity in the frontal and temporal lobes.

The involvement of the system of mamillary bodies and anterior regions of thalami in implementation of generalized seizures was noted in the studies by J. Murphy and J. Gellhorn in 1945 [6] as well as J. Green and F. Morin in 1953 [7].

Most of the studies of the 1940ies carried out with the use of the deep recording and stimulating electrodes demonstrated the existence of different regions in the diencephalic region and the brain stem that have both epileptogenic and antiepileptogenic properties. Later, D. Jinnai et al. [8] have demonstrated an increase in the threshold for seizure activity after destruction of mamillary bodies in an animal model.

The studies of $[^{14}C]2$-deoxy glucose accumulation in pentylenetetrazole-induced seizures identified specific local accumulation of metabolites in the area of mamillary bodies and directly related structures, including anterior thalamic nuclei, mammillothalamic tract, tegmental—mammillary tract, as well as dorsal and ventral nuclei of the pontine tegmentum. This led to a further increased interest of researchers in this anatomical region [9].

In 1987, M. Mirski and J. Ferrendelli [10] published the results of experimental work indicating antiepileptogenic effect of electrolytic destruction of various structures of the Papez’s circuit, including fornix, mammillothalamic tract and mamillary bodies on seizures in guinea pigs caused by pentylenetetrazole administration. Local microinjections of γ-aminobutyric acid analogue muscimol or γ-vinyl-γ-aminobutyric acid (an irreversible inhibitor of γ-aminobutyric acid transaminase) into anterior thalamic nuclei in the studies have also led to a significant increase in resistance to pentylenetetrazole-induced seizures [11, 12].

The study by J. Kusske et al. [13], which was conducted in animals, demonstrated reduction in the frequency and duration of seizures caused by the use of tungstic acid gel for destruction of the ventral regions of anterior thalamus.

C. Hamani et al. [5] described the effect of stimulation and radiofrequency destruction of ANT on pilocarpine-induced seizures and epileptic status. Only bilateral destruction or high-frequency stimulation had anticonvulsant effect in the series of observations, while radiofrequency destruction provided significantly more pronounced effect in the form of increased resistance to generalized seizures.

All of the mentioned studies demonstrated the presence of stable anatomical and functional connections of the mamillary complex and anterior regions of thalami as well as their direct involvement in the process of generalization of pathological epileptic activity.

The only description of destructions of the anterior regions of thalamus with antiepileptic goal in the human in the analyzed literature is the study by S. Mullan et al. [14] published in 1967. The authors presented the results of treatment of 9 patients with intractable epilepsy. In order to perform single-sided destructions, a strontium needle was used, which provided an absorbed dose of 2000 rad (20 Gy) within 15 minutes of exposure at a distance of about 5 mm from the needle tip followed by radiation necrosis of tissues, which was finally formed in approximately a month. According to the presented data, the formed area of radiation necrosis should reach a diameter of about 10 mm. Apparently, determination of the final area of destruction using this method was

### Table 1. Commissural coordinates of anterior thalamic nuclei

<table>
<thead>
<tr>
<th>no. in sequence</th>
<th>Anterior-posterior coordinates</th>
<th>Lateral coordinate</th>
<th>Vertical coordinates</th>
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<td>+10.9</td>
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</table>
impossible due to the unpredictability of tissue reactions to local irradiation and a series of other factors related to the technological features of the method. The calculation of target coordinates, trajectory of the needle dipping and evaluation of destruction area was carried out on the basis of circumstantial data of pneumoventriculography and angiography. Excellent result in the form of complete regression of seizures was achieved in 2 cases of the series, while a significant improvement was noted in 4 patients. The performed intervention had no effect in 1 patient. In 2 cases, patients underwent stereotactic intervention followed by temporal lobectomy, which led to a complete cessation of seizures in 1 patient. It is impossible to reliably determine which intervention resulted in seizure cessation since surgical resection was carried out 11 days after destruction. However, the authors stated that the patient had no seizures in the period between interventions. Complications associated with lesions of the internal capsule and various subcortical structures: hemiparesis, speech disorder and hemianopsia, developed in 6 out of 9 patients; a clinically significant hemorrhage in subcortical nuclei was observed in 1 case.

Unfortunately, neuroimaging data obtained after performed interventions are unavailable. However, the authors note, that, in each case, the damage area included, in addition to anterior thalamic nuclei, internal capsule, lateral group of nuclei, Forel field, mammillothalamic tract and even subthalamic nuclei in some cases.

Thus, it is not possible to judge the accuracy of the performed destructions and antiepileptic efficacy of the destruction of specific anatomical structures presented in the paper.

A significant number of complications that developed due to the lack of neuroimaging and intraoperative neurophysiological monitoring, as well as the inability to simultaneously perform limited in size destruction led to the fact that this method did not get widespread use.

Another factor impeding the widespread use of bilateral destructions of anterior thalamic nuclei was the opinion of some authors that their destruction, especially bilateral, may lead to the formation of severe neurological, including cognitive, deficits e. g. the development of Korsakoff syndrome and Wernicke's encephalopathy [15]. However, a detailed analysis of the MRI data and histological studies in humans presented in this study shows that the damage areas are not confined to the area of anterior thalamic nuclei in the development of alcohol-associated Korsakoff syndrome but involve the medial mamillary nucleus and mediadorsal thalamic nucleus.

There are still some contradictory reports presented in the literature that damage to the thalamus structures and the hypothalamus region in humans leads to memory impairment.

For instance, Y. Van der Werf et al. [16] analyzed the data of MRI and neuropsychological examination of 22 patients with thalamic infarction. A total of 12 patients with concomitant MRI signs of lesions beyond the regions of the thalamus, for example with severe cerebral atrophy or local bilateral hippocampal atrophy, were excluded from the study. Ten patients had different lesions affecting: mammillothalamic tract with a deficit in long-term memory, mediadorsal, median and/or interlaminar nuclei in praxis dysfunction, interlaminar nuclei in complex attention deficit. The authors concluded the involvement of different thalamic nuclei in the formation of certain modalities of memory and attention and a necessity to take into account the existing extra-thalamic lesion in these patients.

The studies in animals have greater specificity. However, their extrapolation to humans is difficult due

### Table 2. Results of surgical treatment

<table>
<thead>
<tr>
<th>no. in sequence</th>
<th>Gender</th>
<th>Follow-up duration, months</th>
<th>Decrease in seizure frequency (%) after 3 months</th>
<th>Decrease in seizure frequency (%) after 6 months</th>
<th>Engel scale of outcomes after 6 months</th>
<th>ILAE scale of outcomes after 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>M</td>
<td>17</td>
<td>—</td>
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<tr>
<td>2</td>
<td>F</td>
<td>16</td>
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<td>100</td>
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<td>3</td>
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<tr>
<td>4*</td>
<td>M</td>
<td>13</td>
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<tr>
<td>5</td>
<td>M</td>
<td>13</td>
<td>95</td>
<td>100</td>
<td>I A</td>
<td>1a</td>
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<tr>
<td>6*</td>
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<td>11</td>
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<td>7</td>
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</tbody>
</table>

*Footnote. * — patients whose follow-up after 3 and 6 months is not available as a result of absenteeism from control studies.
to significant anatomical difference in the structure of the anterior thalamic and hypothalamic areas, as well as their functional significance. Most of such studies were based on the protocol, which does not exclude the spontaneous behavior of rodents.

J. Aggleton and A. Nelson [17] showed in their review paper based on the analysis of a large amount of research data that the influence of destruction of the anterior thalamic nuclei on the formation of the process of memory and attention in animals should be functionally divided into two levels. The first level is a consequence of the destruction of the nucleus and turn off of its various functions. The second level is a consequence of disturbed neuronal activity and plasticity of the structures that are directly associated with ATN, primarily retrosplenial cortex and hippocampus.

The main studies devoted to the identification of the ATN role in impairment of memory and attention processes are based on the study of animal behavior in a maze under different conditions. It has been repeatedly demonstrated that anterior thalamotomy in mice causes disturbed spatial orientation, animals could not reach a sufficient level of precision for the task even in supplementation of the experimental environment with factors improving it. The process of recognition of familiar and new objects was also disrupted. However, the lost functions were eventually partially or fully restored [18, 19].

Further study of the anterior thalamic nuclei led to the understanding of the heterogeneity of their cell structure and function. Thus, it was established that anterodorsal and, to a lesser extent, anteroventral nuclei contain cells responsible for spatial orientation (head direction cells — HD), the structures necessary for the change in the effective behavior under the conditions of changing spatial environment. Serial signals originating in the dorsal nucleus of the tegmentum are projected in the lateral mammillary nuclei and then in anterior dorsal thalamic nucleus, postsubiculum and terminate in the entorhinal cortex [20]. These cells are found in laterodorsal thalamic nucleus, dorsal regions of the striatum, medial regions of the cortex of precentral gyrus (FR2 or AGm region) and CA1 segment of the hippocampus [20]. Such a wide representation in the structures within the Papez’s circuit and beyond it indicates a complex integrative function of these cells in the process of implementation of the spatial orientation and short-term memory.

Analysis of the data of microelectrode recording of neuronal activity in animals and humans demonstrated that 75% of the neurons of the anteroventral and anteromedial nuclei produce constant rhythmic τ–activity in the range of 3—8 Hz, which is projected in the hippocampus and is a key element for the processes of behavioral memory and learning new skills [21].

These studies indicate the undeniable influence of the anterior thalamic nuclei and their connections in the processes of object recognition, memory and attention. However, it should be mentioned again that direct conversion of the results of such studies in rodents to humans is not possible due to significant differences in the anatomic and functional mechanisms of cognitive function formation.

The lack of subjective disorders in the patients of our series associated with the processes of memory and spatial orientation indicates that functions of the anterior thalamic nucleus in humans and their role in the processes of memory and attention formation require further detailed study involving neuropsychologists and advanced neuroimaging techniques.

**Conclusion**

Radiofrequency bilateral anterior thalamotomy is an effective and relatively safe method to monitor epileptic seizures in patients with single and multiple foci of pathological activity located in the frontal and temporal lobes of the brain and with clinically manifested secondary generalized seizures. The use of thermal destruction using a generator of radiofrequency pulses is necessary for establishment of a lesion area controlled in size and localization: it is an important condition for achieving a good result, which we understand as the control over seizures and reduction in the risk of side effects. Intraoperative use of microelectrode analysis with the assessment of ATN activity and neurophysiological boundaries allows stereotactic destruction in this area with maximum accuracy and safety, while reducing the risk of potential complications associated with the damage to nearby structures.

**Authors declare no conflict of interest.**

**REFERENCES**


Commentary

Approximately 1/3 of patients with epilepsy are resistant to drug therapy. In the group of intractable patients, only 1/3 of them has a chance to become candidates for resective surgery and achieve either cessation or reduction in the frequency and severity of seizures. Thus, a large group of patients remain beyond the current capabilities of pharmacotherapy and resective surgery, but it can receive treatment in the form of vagal nerve stimulation or stimulation of the anterior thalamic nuclei. Both methods involve the use of expensive implantable neurostimulation systems. Under these conditions, the selection and development of cheaper treatment methods which are not less effective, of course, are essential both in reduction of treatment costs and also for a wide scope of effective care for patients with intractable epilepsy.

The role of the anterior thalamic nucleus as a target for surgical treatment of epilepsy has been studied since the middle of the twentieth century. Extensive experimental basis and the results of electrical stimulation using implanted electrodes served as the beginning of the clinical use of bilateral stimulation of the anterior thalamic nucleus for the treatment of intractable forms of epilepsy. The effectiveness of bilateral high frequency stimulation of the anterior thalamic nucleus has been demonstrated by a number of studies. Currently, there is at least one randomized controlled trial proving the efficacy and safety of this intervention.

The method proposed by the authors is an experience of the world’s first use of double-sided destruction of the anterior thalamic nucleus for the treatment of patients with intractable epilepsy, and has an essential value for functional neurosurgery. The results of the use of this method were presented at various international conferences and aroused great interest of the experts in the field of functional neurosurgery.

Nevertheless, the study leaves a number of unresolved issues that require further research. Only the early results of the proposed method of surgical treatment have been studied in the majority of patients, while the follow-up period was 6 months only for half of the patients.

In order to fully understand the effectiveness of this method, a long-term observation of patients in the postoperative period is required.

It is advisable to carry out a detailed analysis of the causes of negative results. For example, one patient had a complete lack of effect, while another one showed a 50% reduction in the frequency of seizures, the activity of the anterior thalamic
nucleus was not registered by microelectrode recording in some patients, the length of the registered area of nucleus activity was short in some patients, which did not serve as an occasion for the study of parallel trajectories but, instead of that, resulted in the destruction in the computational field. In these cases, it is advisable to compare localization of destruction foci with the result of surgical treatment.

The authors have their own experience of conducting bilateral stimulation of the anterior thalamic nucleus. It would be interesting to see in the future the results of comparison of the two treatment methods presented in the article.

Further, the statement of the safety of this method is based on the authors’ subjective view on the absence of severe mental disorders after surgery; it is prematurely to talk about the safety of this type of surgery on this basis. Additional study of the neuropsychological status of patients is required. Moreover, the use of special evaluation scales is possible even in the absence of a neuropsychologist.

In summary, it should be noted that this article is a unique study of the world’s first effective use of bilateral destruction of the anterior thalamic nucleus in patients with intractable epilepsy. It is undoubtedly necessary to continue the research for complete and convincing assessment of long-term results and safety of the method.

A.A. Tomskiy (Moscow, Russia)
Neurophysiological Identification of the Cranial Nerves in Endoscopic Endonasal Surgery of Skull Base Tumors

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1Burdenko Neurosurgical Institute, Moscow, Russia; 2Sechenov First Moscow State Medical University, Moscow, Russia

Introduction. Intraoperative identification of the cranial nerves is a useful technique in removal of skull base tumors through the endoscopic endonasal approach. Searching through the scientific literature found one pilot study on the use of triggered electromyography (t-EMG) for identification of the VIth nerve in endoscopic endonasal surgery of skull base tumors (D. San-Juan, et al. 2014).

Objective. The study objective was to prevent iatrogenic injuries to the cranial nerves without reducing the completeness of tumor tissue resection.

Material and methods. In 2014, 5 patients were operated on using the endoscopic endonasal approach. Surgeries were performed for large skull base chordomas (2 cases) and trigeminal nerve neurinomas located in the cavernous sinus (3). Intraoperatively, identification of the cranial nerves was performed by triggered electromyography using a bipolar electrode (except 1 case of chordoma where a monopolar electrode was used). Evaluation of the functional activity of the cranial nerves was carried out both preoperatively and postoperatively.

Results. Tumor resection was total in 4 out of 5 cases and subtotal (chordoma) in 1 case. Intraoperatively, the IIIth (2 patients), VIth (2), and VIIth (4) cranial nerves were identified. No deterioration in the function of the intraoperatively identified nerves was observed in the postoperative period. In one case, no responses from the VIIth nerve on the right (in the cavernous sinus region) were intraoperatively obtained, and deep paresis (up to plegia) of the nerve-innervated muscles developed in the postoperative period. The nerve function was not impaired before surgery.

Conclusion. The t-EMG technique is promising and requires further research.

Keywords: electromyography, intraoperative cranial nerve identification, endoscopic endonasal approach, surgery of skull base tumors.

Abbreviations
EMG — electromyography
CNs — cranial nerves
f-EMG — (free run) spontaneous EMG
t-EMG — triggered EMG
CT — computed tomography
MRI — magnetic resonance imaging
SCT — spiral computed tomography
TBD — total boost dose
DM — dura mater
ICA — internal carotid artery

An intraoperative CN identification technique enables modification of a surgical approach and reduces the risk of postoperative complications associated with any effects on the nerves. A reduced amplitude of evoked potentials and changes in the M-response parameters in the course of surgery have adverse prognostic significance for the functioning of both the nerves and the muscles innervated by them [1—3].

Currently, two main techniques are used for identification of the motor CNs: triggered EMG (t-EMG) — an EMG mode synchronized with electrical stimulation; free run EMG (f-EMG) — spontaneous EMG. Cranial nerve monitoring by f-EMG is continuous detection of the spontaneous electromyographic activity that is characterized by changes such as spikes, bursts, and neurotonic discharges accompanying mechanical contact of any tool with the CNs. The triggered EMG mode is a technique to record the compound muscle action potential (CMAP) that occurs in response to electric stimulation of the nerve trunk (M-response).

Recent published studies in this area, which we could find in the available literature, were conducted by P. Thirumala et al. [4, 5] in 2012—2013 and D. SanJuan et al. [6] in 2014. In 2012, P. Thirumala et al. [4] reported 78 surgeries for skull base tumors using the endoscopic endonasal approach and f-EMG for intraoperative CN monitoring. In 2013, P. Thirumala et al. [5] conducted another study to evaluate significance of the f-EMG technique, which included 200 surgeries for skull base tumors performed through the endoscopic endonasal approach. On the basis of the obtained data, the authors concluded that the use of f-EMG for cranial nerve identification is not a sufficiently sensitive technique. According to the authors [5], application of t-EMG may be more promising.

A pilot study by D. San Juan et al. [6] in 8 patients demonstrated that the t-EMG technique in endoscopic endonasal surgery for skull base tumors seems to be safe and promising.

The rate of iatrogenic injuries in surgery for skull base tumors performed through open (transcranial) or endoscopic endonasal approaches using different methods is high, which is why it is usually necessary to use CN monitoring.
techniques of intraoperative CN identification is 2 to 47% [2, 4, 7—10]. In the absence of neurophysiological identification, the rate of CN injuries is 14 to 68%. Injury to the VIth and VIIth cranial nerves is the most frequent complication in the postoperative period [7, 9, 11].

In this regard, the problem of intraoperative CN identification in endoscopic transnasal surgery is very topical.

The purpose of this work is to develop an algorithm of neurophysiological CN identification in endoscopic endonasal surgery for skull base tumors, which ensures anatomical and functional integrity of the CNs without reducing the completeness of tumor resection.

Material and Methods

Our pilot study included 5 patients operated on through the endoscopic endonasal approach using neurophysiological identification at the Burdenko Neurosurgical Institute in 2014 (Table 1).

The patient selection criteria were as follows:

— skull base tumors with laterosellar and retrosellar spread;
— features of the topographic and anatomic localization of the tumor and an associated risk of intraoperative iatrogenic injury to the CNs;
— a preoperative functional CN deficit.

The study included patients in whom intraoperative neurophysiological identification of at least one cranial nerve had been performed.

The patient’s neurological status (including functional CN activity) was assessed before and after surgery.

A scale proposed by Prof. N.K. Serova et al. in 2011 was used in physical examination of oculomotor nerve functions. The authors proposed to evaluate each eye movements upwards, downwards, and sideways on a scale of 0 to 5. The absence of impairments (norm) was scored 0. A slightly restricted movement was scored 1; a movement restricted by 1/3 was scored 2; a movement restricted by 1/2 was scored 3; a movement restricted by 1/3 was scored 4; the lack of voluntary eye movements was scored 5. The presence and severity of ptosis was also scored 0 to 5 [12].

The completeness of tumor resection was evaluated on a scale proposed by G. Frank and E. Pasquini [13]:

— radical resection is characterized by the absence of tumor signs on control CT and/or MRI scans;
— subtotal resection is that when the residual tumor is less than 20% of the initial tumor;
— partial resection is that when the residual tumor is less than 50% of the initial tumor;
— insufficient resection is that when the residual tumor is 50% and more of the initial tumor.

Neurophysiological CN identification was used intraoperatively. Surgeries were performed for large skull base chordomas (2 cases) and trigeminal nerve neurinomas located in the cavernous sinus (3).

An 8-channel Viking Select electromyograph system (Nikolet, USA) was used for neurophysiological CN identification. Bi- and monopolar stimulating probes were used for CN identification [14—16].

When a bipolar electrode is used, the anode and cathode are placed in the close proximity to each other. This minimizes current propagation to surrounding tissues, which provides a more accurate identification of the CN location (Fig. 1a).

In the case of a monopolar electrode, current propagates in the fan-shaped manner, with a higher gradient than from a bipolar electrode, which covers a larger tissue segment compared to a bipolar electrode; however, the location accuracy in this case is significantly lower (Fig. 1b).

The advantages of bipolar stimulation of neural tissue include the lack of electrolytic lesions [17] and, most importantly, a much lower amplitude of the stimulation artifact due to the absence of electrode and tissue polarization. A feature of the bipolar stimulating electrode also is that stimulation occurs to the same extent under both electrodes because each of the electrodes alternately becomes the cathode and the anode as a pulse passes [2].

A technique of intraoperative cranial nerve identification

Anesthesia care

A total intravenous anesthesia (TIVA) technique was used as anesthesia care in all performed surgeries:

— premedication: 0.3—0.5 mg of atropine, iv; 2 mg of tavegil, iv; 2.5 mg of dormicum, iv;
— induction: 2 mg/kg of propofol, bolus, iv; 2.5 µg/kg of fentanyl, iv;
— maintenance of surgical anesthesia: continuous infusion of 4—7 mg/kg/h of propofol and 0.01 µg/kg/h of fentanyl.

An intermediate-acting muscle relaxant, 0.6 mg/kg of rocuronium, was used for tracheal intubation.

Table 1. A distribution of patients by the gender, histologic diagnosis, tumor localization, and used surgical approach

<table>
<thead>
<tr>
<th>Chordoma</th>
<th>Neurinoma</th>
<th>Surgical approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>Posterior extended (transclival)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total 5</td>
<td>Total 5</td>
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</table>

Table 1. A distribution of patients by the gender, histologic diagnosis, tumor localization, and used surgical approach
electrode for the V (ground) was placed on the chin, and the reference identification of the facial nerve. A zero electrode abducent nerve, and in the orbicular muscle of the eye for the external rectus muscles for identification of the muscles for identification of the trigeminal nerve, into were placed in the superior and inferior rectus muscles.

Neurophysiological technique, needle electrodes were placed percutaneously in the muscles innervated by the III nerve of interest to the neurosurgeon (Table 2).

Table 2. Muscles used to place electrodes for neurophysiological identification of cranial nerves

<table>
<thead>
<tr>
<th>CN</th>
<th>Muscles</th>
<th>CN</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Rectus medialis</td>
<td>VII</td>
<td>Orbicularis oculi</td>
</tr>
<tr>
<td></td>
<td>Rectus inferior</td>
<td></td>
<td>Orbicularis oris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IX</td>
<td>Stylopharyngeus</td>
</tr>
<tr>
<td>IV</td>
<td>Obliquus superior</td>
<td>X</td>
<td>Vocalis</td>
</tr>
<tr>
<td>V</td>
<td>Digastricus</td>
<td>XI</td>
<td>Trapezius</td>
</tr>
<tr>
<td></td>
<td>Masseter</td>
<td></td>
<td>Sternocleidomastoideus</td>
</tr>
<tr>
<td>VI</td>
<td>Rectus lateralis</td>
<td>XII</td>
<td>Hypoglossus</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Genioglossus</td>
</tr>
</tbody>
</table>

**Preparation**

To conduct the study according to a conventional electrophysiological technique, needle electrodes were placed percutaneously in the muscles innervated by the nerve of interest to the neurosurgeon (Table 2).

To identify the oculomotor nerve, needle electrodes were placed in the superior and inferior rectus muscles.

Needle electrodes were placed in the mastication muscles for identification of the trigeminal nerve, into the external rectus muscles for identification of the abducense nerve, and in the orbicular muscle of the eye for identification of the facial nerve. A zero electrode (ground) was placed on the chin, and the reference electrode for the V and VI nerves was placed at Fpz.

**Stimulation**

We used rhythmic electrical simulation by single pulses with a frequency of 4.7 Hz and a stimulus duration of 0.1 ms. The current strength was varied from 2 to 16 mA. We used a coaxial bipolar stimulating electrode (GVB-geliMED FG, Germany) (Fig. 2), the configuration of which could be intraoperatively changed without interrupting electrical conductivity of the electrode.

**Recording of motor muscle responses**

We used t-EMG with an epoch (time base) of 20 ms/point and sensitivity of 50 µV/point.

Given the availability of only one publication in the international literature on the use of t-EMG for CN identification in endoscopic endonasal removal of skull base tumors, it seems appropriate to present our clinical cases to colleagues.

**Clinical case 1**

A 63-year-old patient T. presented with trigeminal nerve neurinoma in the right cavernous sinus (Fig. 3). Clinically, the tumor manifested as paresis of the muscles innervated by the III and Vth nerves on the right. The range of eyeball movements was evaluated as follows: upwards — 4 points, inwards — 4 points, downwards — 3 points, and outwards — 4 points.

Neurophysiological CN identification was performed at initial steps of tumor removal. M-responses were obtained from the muscle innervated by the right Vth nerve on the right (stimulus strength of 4–8 mA). Manipulations for tumor removal were conducted more carefully in the M-response region (presumably, the localization area of the Vth cranial nerve) to prevent injury to the identified nerve. Visualization of the nerve failed because it was probably displaced by the tumor and/or grossly thinned. No visible tumor residuals were detected at the end of surgery. At the final steps of tumor removal, we performed control nerve identification, during which M-responses were obtained from the previously identified nerve, which indicated its integrity. Identification of the IIIrd and VIth nerves failed.

Control examinations on the 7th day after surgery revealed persistent paresis of the muscles innervated by the IIIrd nerve on the right and worsening of paresis (to plegia) of the muscles innervated by the VIth nerve on the right. Weakness of the Vth nerve also retained. The range of right eye movements was as follows: upwards — 4 points, inwards — 2 points, downwards — 2–3 points, and outwards — 5 points. A follow-up examination revealed regression of oculomotor impairments: upwards — 3–4 points, downwards — 2–3 points, inwards — 2–3 points, and outwards — 0 points.

MRI performed 6 months after surgery showed complete tumor resection (Fig. 4).

**Clinical case 2**

A 50-year-old patient Sh. presented with continued growth of clival chordoma (Fig. 5). Before admission to the Neurosurgical Institute, the patient underwent two surgeries using transcranial (2013) and transnasal (2014) approaches, which were performed at another clinic. Clinically, the tumor manifested as paresis of the muscles innervated by the right oculomotor nerve and weakness of the right abducense nerve: movement restriction was scored 4 points (upwards), 1—2 points (inwards), 1 point (downwards), and 2 points (outwards).

Because the tumor tended to extend laterosellarly to both sides (more to the right), we started tumor removal with laterosellar identification of the CNs, from two sides. At this step of surgery, visualization of the nerves failed.

We performed neurophysiological identification of the CNs that had not been visualized. Upon monopolar...
stimulation with stimulus strength of 4—6 mA through the tumor, we obtained high amplitude M-responses (presumably from a depth of about 15 mm) from the muscles innervated by the IIIrd cranial nerve on the right and low amplitude responses from the IIIrd cranial nerve on the left as well as from the VIth cranial nerve on the left. Because of the nerve proximity, further manipulation for tumor removal in this area was performed more carefully. The tumor was completely resected. Control identification after tumor resection detected clear M-responses, which indicated functional preservation of the identified nerves.

A follow-up examination 3 months after surgery showed regression of IIIrd nerve paresis on the right: upwards — 4 points, outwards — 2 points, downwards — 0 points, and inwards — 0 points.

MRI 10 months after surgery demonstrated complete tumor resection (Fig. 6).

Clinical case 3

A 49-year-old patient B. was admitted with a large trigeminal nerve neurinoma in the left cavernous sinus (Fig. 7). According to the medical history, the patient underwent radiotherapy with TBD of 60 Gy on a Novalis apparatus (the patient refrained from proposed surgery) in January 2012. In the autumn of 2012, MRI revealed a reduction in the tumor size. The tumor continued to decrease until March 2013. However, in the autumn of 2013, MRI showed an increase in the tumor size. In April 2014, MRI and SCT confirmed a further increase in the tumor size. At patient’s admission to the Burdenko Neurosurgical Institute, the tumor manifested as superior orbital fissure syndrome on the left: oculomotor impairments in the form of paresis of the IIIrd, IVth, and VIth nerves on the left (range of movements was severely restricted in all directions to 4—5 points). Also, there was left-sided exophthalmos of 2 mm.

During surgery, we additionally used an ultrasonic sensor for external detection of the ICA, which was an important step to avoid iatrogenic injury to the artery during DM opening in the cavernous sinus region through an extended lateral approach. The detection was carried out in all similar cases. The left wall of the cavernous sinus was open inferiorly and more laterally to the area of the left ICA location (Fig. 8); a cystic part of the tumor was emptied.

ICA detection not only before opening the antero-external wall of the cavernous sinus but also in the sinus cavity is an important step in the intervention, which enables avoiding injury to the cavity (Fig. 9). During tumor resection and isolation of the ICA in the cavernous sinus cavity upon stimulation through the tumor mass at relatively high motor thresholds of 9—10 mA, M-responses were obtained from a depth of about 5 mm (tumor thickness in the area of electrical simulation was ≈ 5 mm) from the muscles innervated by the Vth nerve on the left (Fig. 10). Visualization of the Vth nerve failed because the nerve was probably displaced by the tumor and grossly thinned. After tumor resection, stimulation in the outer parts of the cavernous sinus provided clear M-responses from the muscles innervated by the VIth nerve on the left; the nerve also was not visualized. The M-responses indicated preservation of the CNs.

Control MRI 3.5 months after surgery showed complete tumor resection (Fig. 11).
A control examination by neuro-ophthalmologist before discharge revealed regression of oculomotor impairments: downwards — 4—5, outwards and upwards — 3 points, and inwards — 2 points. Exophthalmos also regressed. An examination by neuro-ophthalmologist after 3 months demonstrated further regression of oculomotor impairments: eye movements upwards — 2—3 points, inwards — 0—1, downwards — 3—4 points, and outwards — 4 points. The intraoperatively identified Vth was functionally preserved.

Fig. 4. Case 1.
MRI scans of the 63-year-old patient T. 6 months after surgery. Complete tumor resection.

Fig. 5. Case 2.
MRI scans of a 50-year-old patient Sh. before surgery. A large chordoma of the upper and middle parts of the clivus, grossly compressing the pons, is seen.
**Clinical case 4**

A 72-year-old patient M. was admitted with a skull base chordoma destroying the clivus almost throughout all its length and extending supra- and latero(D, S) sellarly to the supero-medial regions of the right orbit as well as to the nasopharynx (Fig. 12).

The clinical picture was characterized by gross chiasmal syndrome with a large impact on the right optic nerve. The visual acuity was as follows: Vis OD — finger counting from 30 cm, Vis OS — 0.6. There were no movements of the left eye upwards, downwards, to the nose (5 points — plegia of the muscles innervated by the IIIrd nerve); outwards movements were preserved — 0 points (the VIth nerve was functionally preserved). There were no oculomotor impairments on the right. The patient also had decompensated type 2 diabetes mellitus and hypertension. Neurophysiological CN identification was performed during removal of the tumor from both cavernous sinuses. Bipolar rhythmic electrical simulation with 8 mA current provided clear M-responses from m. rectus lateralis dex. at sin., which enabled identification of the VIth cranial nerve localization, first on the right and then on the left (Fig. 13). We tried to identify the IIIrd nerve on both...
Fig. 8. Opening of the left cavernous sinus dura, laterally to the previously identified carotid artery.
The yellow dotted line designates a supposed line of DM size. The white dotted line designates the projection of the previously located ICA.

Fig. 9. Ultrasonic detection of the ICA in the cavernous sinus cavity.
White dotted lines designate the ICA projection.

Fig. 10. Neurophysiological identification of CNs in the structure of tumor tissue.
Stimulation in the area marked by the yellow dashed line evoked M-responses from the Vth cranial nerve.

Fig. 11. Case 3.
A SCT scan of a 49-year-old patient B. 3 months after surgery. Complete tumor resection sides, but no M-responses were obtained, probably due to degenerative nerve damage caused by the tumor. Because a part of the tumor, which was intimately adjacent to and tightly encased the ICA, was very dense and also encased the neurophysiologically identified nerves, we decided to resect the tumor subtotally to avoid a conflict with the above anatomical structures.

An examination 3 months after surgery revealed persistence of oculomotor impairments at the preoperative level. MRI 4 months after surgery demonstrated a residual tumor growing over the left ICA (Fig. 14).

Clinical case 5

A 59-year-old patient Z presented with trigeminal nerve neurinoma in the right cavernous sinus region (Fig. 15). The tumor manifested as growing hypoesthesia in the projection of all three branches of the Vth nerve on the right, decreased corneal reflex on the right, and pronounced headaches.

Electrophysiological CN identification was performed during tumor resection. Branches of the right trigeminal nerve were clearly identified (Fig. 16a); also, a fuzzy signal from the right VIth nerve was obtained. After tumor resection, repeated identification provided a response from the previously identified Vth and VIth nerves on the right.

Visualization of the neurophysiologically identified nerves failed. A control examination by the ophthalmologist revealed improvement in the function of the Vth nerve on the right.

MRI 6 months after surgery demonstrated complete tumor resection (Fig. 16b).
Results

In 2014, we operated 5 patients using the endoscopic endonasal approach. All the patients underwent intraoperative identification of the CNs by t-EMG: 2 patients had chordomas, and 3 patients had trigeminal nerve neurinomas. The extended lateral approach was used in 4 cases, and the posterior extended transclival approach was used in 1 patient.

In all cases, except case 2 (skull base chordoma), we used a coaxial bipolar electrode for CN identification. Intraoperatively, at least one cranial nerve was neurophysiologically identified in each case: the IIIrd nerve was identified in 2 patients; the Vth nerve was identified in 2 patients; the VIth nerve was identified in 4 patients (Table 3). Identification was performed both during and after resection of the tumor. In 4 cases, the tumor was removed completely. In 1 case, resection was subtotal (case 4), which was due to a dense structure of the tumor and intimate adherence to the intracavernous part of the left ICA. In the postoperative period, no deterioration in functions of the intraoperatively identified nerves occurred in all the cases. In 1 case (case 1), a deficit of the VIth nerve was observed in the postoperative period; in this case, no M-response was intraoperatively detected during the active search for the nerve in the surgical wound (Table 4). To prevent postoperative cerebrospinal liquid leakage, skull base reconstruction was performed in all cases using the fascia lata, a bony part of the nasal septum, adipose tissue, and fibrin-thrombin glue.

Discussion

During surgery, we applied a t-EMG-based technique of CN identification. The essence of the technique is to feed an electrical pulse to a CN and to detect M-responses from the muscles innervated by the nerve. The absence of M-responses upon feeding a pulse to a CN may be a sign of complete nerve trunk injury. However, if M-responses are evoked only at increased current strength, this indicates partial nerve injury and may be a predictor of a postoperative deficit [18]. M-responses can not be evoked by a pulse of standard current strength applied aside from a nerve. The exact identification of the CN location in the surgical wound enables avoiding iatrogenic injuries due to an adequate modification of a surgical technique before contacting the nerve trunk, without reducing the extent of tumor tissue resection.

The technique of CN identification has been developed and improved for many years and currently seems to be important and promising, as evidenced by a number of studies.

A study by L. Sekhar [10], which was devoted to intraoperative monitoring of the oculomotor nerves (in transcranial approaches), demonstrated that the t-EMG technique is promising for this purpose and useful in work of the surgeon. In 1992, T. Sekiya et al. [19] reported on application of the t-EMG technique for identification of all oculomotor nerves in 18 transcranial surgeries for tumors in the cavernous sinuses. On the basis of these results, the technique was concluded to be highly efficient in skull base surgery.

In 1995, J. Maurer et al. [8] published the data from a study devoted to identification of the CNs (mainly the VIIth nerve) using t-EMG during surgeries for auditory nerve neurinomas. The authors noted that intraoperative monitoring is a useful technique in skull base surgery, which enables quick and safe identification of the CNs, especially under conditions of the diseased anatomy.

G.A. Shchekut’ev, A.N. Konovalov, et al. [20] demonstrated importance of the technique for monitoring...
Fig. 13. Case 4.
a — identification of the VIth cranial nerve on the right. Electrical stimulation in the right cavernous sinus cavity evoked clear M-responses from the right lateral rectus muscle; b — identification of the VIth cranial nerve on the left. Electrical stimulation in the left cavernous sinus cavity provided clear M-responses from the left lateral rectus muscle of the eye; c — the right cavernous sinus — intraoperative identification of the VIth cranial nerves. The white dotted line designates the ICA in the cavernous sinus. The yellow dotted line designates the area of neurophysiological identification of the VIth cranial nerve; d — the left cavernous sinus — intraoperative identification of the VIth cranial nerves. The yellow dotted line designates the area of neurophysiological identification of the VIth cranial nerve.

Fig. 14. Case 4.
MRI scans of the 72-year-old patient M. 4 months after surgery: a small residual tumor encasing the left ICA is seen.
Fig. 15. Case 5.
a — a SCT scan of a 59-year-old patient Z. before surgery: a medium-sized tumor with calcifications is seen in the right cavernous sinus area; b — MRI scans of the 59-year-old patient Z. before surgery: the tumor of the right cavernous sinus.

Fig. 16. Case 5.
a — identification of the IIIrd, VIth, and Vth cranial nerves on the right, clear M-responses from muscles innervated by the Vth cranial nerve are obtained; b — a MRI scan of the 59-year-old patient Z. 6 months after surgery. Complete tumor resection.

Table 3. Identified nerves and current parameters

<table>
<thead>
<tr>
<th>Cranial nerve</th>
<th>III</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients who underwent nerve identification</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Number of identified CNs</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mean current strength, mA</td>
<td>4–6</td>
<td>4–10</td>
<td>4–10</td>
</tr>
<tr>
<td>Stimulation frequency, Hz</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Stimulus duration, ms</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

data with those of a control group of 26 surgeries without neurophysiological identification: a postoperative deficit of the oculomotor nerves occurred in 6 (23%) cases.

In our study, obtained M-responses were classified as strong and weak. To simplify processing of the obtained data, we designated a weak M-response as 0 and a strong M-response as 1 (Table 4). Detection of weak M-responses was a signal to the surgeon to be more careful in resecting the tumor because of a risk of injury to the nerve trunk or its relative proximity.

In our study, a deficit of the VIth nerve in the postoperative period occurred only in 1 case (case 1).
<table>
<thead>
<tr>
<th>Case</th>
<th>Histologic diagnosis</th>
<th>Localization</th>
<th>Preoperative symptoms</th>
<th>Approach</th>
<th>Lumbar drainage</th>
<th>Tumor resection complete</th>
<th>Cranial nerve identification</th>
<th>Postoperative complications</th>
<th>M-response parameters: 0 — weak response, 1 — strong response</th>
<th>Changes in symptoms. Evaluation of oculomotor functions</th>
<th>3 months after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1, 63-year-old patient</td>
<td>Trigeminal nerve neurinoma</td>
<td>Right cavernous sinus</td>
<td>Paresis of the III° nerve on the right: upwards — 4 points, downwards — 3 points. Weakness of the V° nerve on the right</td>
<td>Extended lateral</td>
<td>Beginning of surgery</td>
<td>Surgery end</td>
<td>Radical</td>
<td>V° nerve, right</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Case 2, 50-year-old patient</td>
<td>Chordoma</td>
<td>Clival region</td>
<td>Lesion of the right-II° nerve and weakness of the right VP° nerve: upwards — 4 points, downwards — 1 point, outwards — 2 points, inwards — 1–2 points</td>
<td>Posterior extended transclival</td>
<td>Beginning of surgery</td>
<td>3° post-operative day</td>
<td>Radical</td>
<td>III° nerve, right; weak response, left; VI° nerve, right</td>
<td>No</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Case 3, 49-year-old patient</td>
<td>Trigeminal nerve neurinoma</td>
<td>Left cavernous sinus</td>
<td>Lesion of the III°, IV°, and VI° nerves on the left (4—5 points)</td>
<td>Extended lateral</td>
<td>Beginning of surgery</td>
<td>Surgery end</td>
<td>Radical</td>
<td>V° and VI° nerves, left</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Case 4, 72-year-old patient</td>
<td>Chordoma</td>
<td>Endo-infra-supralatero (D, S) sellar region</td>
<td>Chiari syndrome: lesion of the left III° nerve: upwards, downwards, and inwards — 5 points, outwards — 0 points</td>
<td>Extended bilateral transclival</td>
<td>Beginning of surgery</td>
<td>5° post-operative day</td>
<td>Subtotal</td>
<td>VI° nerve bilateral</td>
<td>No</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Case 5, 59-year-old patient</td>
<td>Trigeminal nerve neurinoma</td>
<td>Right cavernous sinus</td>
<td>Hypoesthesia in the projection of all three branches of the V° nerve on the right</td>
<td>Extended lateral</td>
<td>Beginning of surgery</td>
<td>Surgery end</td>
<td>Radical</td>
<td>III° and VI° nerves, right</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
</tbody>
</table>
Intraoperatively, we could not obtain M-responses from the lateral rectus muscle of the eye; in the postoperative period, complete paralysis of the muscle developed. It is worth noting that the abducent nerve function was not compromised before surgery. The function of the nerves that were intraoperatively identified, even in the case of weak M-responses, did not get worse, but improved in many cases (Table 4). Given our findings, we may draw a preliminary conclusion about a high predictive value and usefulness of the technique in prevention of iatrogenic injuries.

Intraoperative CN identification in our study did not reduce the extent of tumor resection. Tumor resection was assessed as complete in 4 of 5 cases and as subtotal in 1 case. In the latter case, the causes for subtotal tumor resection were intimate adherence of the tumor to the intracavernous part of the ICA as well as the presence of the identified VIth nerve inside the solid tumor; therefore, subtotal resection was chosen.

Visualization of the CNs during endoscopic endonasal surgery for skull base tumors is not always possible because of the tumor influence on the nerves. The nerves can be flattened by the tumor, ischemized, or grossly adherent to the tumor; therefore, the topographic and anatomic relationships in the surgery site may be altered. Only neurophysiological CN identification during tumor resection provides the anatomic and functional integrity of the nerves and navigation in the diseased anatomy.

If no M-responses are obtained during identification, more aggressive tumor resection is performed. When significant M-responses are detected, the surgeon should try to visualize the CNs and use a more careful tactics for tumor resection. On the basis of our personal experience (more than 1,200 endoscopic endonasal surgeries), we believe that a tumor fragment very tightly adherent to the CN should be spared to avoid nerve injury.

Determination of a depth of CN occurrence inside the tumor is very important. Unfortunately, exact determination of the depth of CN occurrence is impossible at present; however, neurophysiological identification makes it possible to determine the CN topography, which may indirectly be used to measure an approximate depth of nerve occurrence. In this case, it is necessary to allow for the minimum current, at which M-responses can be evoked, and the amplitude of M-responses.

Also, to determine the depth of CN occurrence, it is necessary to allow for the biophysical characteristics of the tumor: electrical conductivity, density, and degree of vascularization. Currently, these properties of tumors (in particular, chordomas and neurinomas) are not investigated.

In our opinion, one of the possible ways to modify the used technique is monitoring of corticobulbar motor-evoked potentials.

Surgeries were performed using a two-dimensional (2D) endoscope. It seems that implementation of a stereo endoscope (3D) in practice is the most promising way to further improve visualization of a surgical object.

In the future, we plan to conduct a comparative analysis of surgical treatment outcomes between a group of patients who have undergone CN identification and a control group where CN identification has not been performed for various reasons.

**Conclusion**

Our pilot study suggests that t-EMG may be a promising and safe technique for CN identification in endoscopic endonasal resection of extended skull base tumors, which provides the anatomic and functional integrity of the CNs without a forced reduction in the extent of tumor resection and may also help determine the boundary of physiological limits of surgery. Further studies, of course, will require accumulation of the clinical data and their statistical and comparative analysis.

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Authors declare no conflict of interest.

**REFERENCES**


Actively developing endoscopic endonasal surgery of skull base tumors using extended approaches is a classic example of the integrated use of innovative minimally invasive techniques in neurooncology. A comprehensive analysis of publications devoted to application of modern minimally invasive techniques in endonasal surgery for skull base tumors indicates a small number of studies related to integration and differentiated use of intraoperative video endoscopy and electrophysiological identification of the cranial nerves in resection of these tumors. Given that the vast majority of skull base tumors are currently resected through the endoscopic endonasal approach, in-depth research in this area is very topical.

The most important component of a complex intraoperative diagnosis is electrophysiological cranial nerve identification aimed at preventing iatrogenic nerve injuries, the rate of which without application of this technique amounts to 14—68% of cases [V.A. Cherekaev et al., 2010; S.Q. Liang et al., 2012; B. Wu et al., 2013]. In this regard, the use of intraoperative triggered electromyography for mapping of the cranial nerves in endoscopic endonasal surgery of skull base tumors seems very promising. D. San Juan et al. presented in their paper the results of a pilot study that confirmed this technique in endoscopic endonasal surgery of skull base tumor using extended approaches. In 2014, A.N. Shkarubo et al. published, for the first time in the Russian literature, the results of application of intraoperative triggered electromyography (t-EMG) for identification of the cranial nerves in 5 patients with skull base tumors who were operated on using the endoscopic endonasal approach at the Burdenko Neurosurgical Institute in 2014.

In this case, the patient selection criteria were formulated for the first time, which included: 1) skull base tumors with latero- and retrosellar extension; 2) features of the topographic and anatomic localization of the tumor and, as a consequence, the risk of possible intraoperative iatrogenic injuries to the cranial nerves; 3) preoperative nerve injuries.

It is generally known that direct visualization of the cranial nerves during endoscopic endonasal surgery for skull base tumors is usually complicated due to compression and/or invasion by the tumor and changes in the intracranial topographic and anatomic relationships. In this situation, the technique of choice to ensure the anatomical integrity and functional preservation of the cranial nerves is electrophysiological nerve identification.

The problem of determining the depth of cranial nerve occurrence in tumor tissue still remains debatable, which affects the choice of an optimal surgical approach and the extent of surgical cytoreduction.

We agree with the authors’ opinion about the prospects of intraoperative monitoring of corticobulbar motor evoked potentials and extending the capabilities of intraoperative visualization through the use of 3D-stereo endoscopy in endonasal removal of skull base tumors. The results of this national pilot study indicate optimization of the surgical technique and a reduced risk of postoperative cranial nerve injuries.

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22. http://dx.doi.org/10.1097/00006123-199306000-00012
Surgery of skull base tumors is one of the most complex and, therefore, challenging areas of neurosurgery. One of the many challenges faced by the surgeon in the course of his work is identification of landmarks in the wound. This is especially true for diffuse processes: infiltrating tumors causing destruction of the normal anatomic, in particular bone, structures. The use of navigation systems (optical, electromagnetic, ultrasonic, and even metabolic) only partially solves the problem.

Nerve identification techniques are used in many areas of surgery, including neurosurgery, for intraoperative visualization and preservation of the nerve trunks. The first experimental works on this subject were carried out in the 1950s (A. Iggo et al.). One of these techniques is electromyography that has been developed and implemented in identification of the peripheral nerves (Shedd; Durham et al.) and then become widely used to locate the facial nerve in surgery of cerebellopontine angle tumors.

This technique has been applied for identification of the oculomotor nerves in the orbit and cavernous sinus for more than 20 years, but is not widely used. Free-run electromyography has low sensitivity, while triggered electromyography is an imperfect technique that increases the duration of surgery, requires additional technical equipment, often is uninformative, and has no significant positive effect on the postoperative clinical outcome.

However, interest to the technique is now renewing in the context of a changed surgical paradigm. This is primarily associated with the development of adjuvant therapies that make it possible to renounce radical surgery in favor of minimally invasive interventions preserving the patient’s quality of life, followed by control of residual tumor growth.

In addition, previously published studies mainly described application of the EMG technique in transcranial surgery with detection of a muscle response directly from the oculomotor muscles in the surgical wound. The development of endoscopic surgery of the chiasm-sellar region, cavernous sinus, and orbit has greatly increased the capabilities of transnasal surgery. A few publications described application of the EMG technique, which was modified for an endonasal intervention, for oculomotor nerve identification in endoscopic surgery. Application of triggered EMG in transnasal surgery has not been described; however, given the renewed interest in the technique at opinion-leader centers of transnasal surgery, a series of publications devoted to this technique may be expected in the near future.

The work by A.N. Shkarubo et al., making no pretense to identification of any statistical patterns, demonstrates the technique's capabilities and holds out a hope that a full study with a sufficient number of patients will demonstrate a significantly lower postoperative deficit in patients treated with the technique compared to that in a control group.

Yu.A. Shcherbyuk (St. Petersburg, Russia)

Commentary

Surgery of skull base tumors is one of the most complex and, therefore, challenging areas of neurosurgery. One of the many challenges faced by the surgeon in the course of his work is identification of landmarks in the wound. This is especially true for diffuse processes: infiltrating tumors causing destruction of the normal anatomic, in particular bone, structures. The use of navigation systems (optical, electromagnetic, ultrasonic, and even metabolic) only partially solves the problem.

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V.A. Cherekaev, N.V. Lasunin (Moscow, Russia)
Neuroblastoma (NB) is the most common extracranial solid tumor in children. The neoplasm grows from progenitor cells of the sympathetic nervous system and can be detected anywhere along the sympathetic neurological circuit: retroperitoneally, mediastinally, cervically, and pelvically. Examination of children with suspected neuroblastoma is comprehensive and performed in strict compliance with a therapeutic protocol. A decision on the treatment regimen is made based on the tumor staging and the risk group of the patient. The diagnosis and treatment of NB patients are comprehensive and can be fully carried out only at the pediatric oncology department. In 10-15% of cases, an hourglass tumor spreads to the intervertebral foramina or spinal canal at one or more levels. A tumor node is always located extradurally with respect to the spinal cord. Symptoms of spinal cord compression of various severity are observed in 5-7% of patients. We present several cases of patients with neuroblastoma with intraspinal extension. Despite apparent benefits of primary surgical decompression of the spinal cord, modern experience of treatment of children with intraspinal tumor extension does not reveal advantages of surgery over chemotherapy. Neurological disorders of various nature and severity persist in the majority of patients in the long-term period, regardless of primary treatment. A higher level of spinal deformities after surgical tumor resection is observed. The issue of spinal cord decompression should be discussed by the neurosurgeon and pediatric oncologist, and the most common method of choice may be chemotherapy. The article discusses the indications and contraindications for neurosurgical interventions in NB patients and addresses the issues of NB metastasis to the brain and cranial bones as well as the opsoclonus-myoclonus syndrome.

**Keywords:** neuroblastoma, spinal cord compression, spinal cord tumor, chemotherapy.
choice for a benign type of tumor, ganglioneuroma [2—4].

The prognosis of NB is primarily determined by the patient’s age and stage of the disease, and young age is a favorable factor. The survival of patients with localized NB (stage I and II) is more than 90%, for stage III survival decreases to 50–60%, and for stage IV to 5–10%. A high-dose polychemotherapy combined with autologous bone marrow transplantation improves the 2-5-year relapse-free survival of children with NB stage IV to 30%. It should be noted a favorable prognosis for stage IVS in children under one year. In these cases, in addition to primary tumor usually localized in the adrenal gland, the liver and bone marrow metastases can be detected, but without skeletal lesions [2—4].

Thus, diagnosis and treatment of NB patients are comprehensive and can be fully carried out only at the pediatric oncology department.

Intraspinal extension of neuroblastoma

In some cases, the manifestation of NB includes neurological symptoms, and neurosurgeons are the first doctors who advise the patients.

In 10–15% of cases, an hourglass tumor spreads to the intervertebral foramina or spinal canal at one or more levels. A tumor node is always localized extradurally with respect to the spinal cord. The symptoms of spinal cord compression of various severity are observed in 5–7% of patients and include the back pain, paraparesis or paraplegia, pelvic organs dysfunction and sensory disorders. The symptoms may be acute, but more often develop gradually over many weeks or even months [5, 6]. Sometimes spinal symptoms are detected at birth [7].

Clinical manifestations of the spinal cord compression require an immediate medical care because the possibility of neurological function recovery is higher, the faster the spinal cord decompression is performed. However, the tumor nodule can be removed with neurosurgery or chemotherapy which can cause a decrease in the tumor size and even its disappearance. The optimal treatment strategy is actively discussed in the literature.

We present the clinical cases of epidural spinal cord compression in NB patients treated in Dmitry Rogachev Federal Scientific Centre of Hematology, Oncology and Immunology.

Clinical case No. 1

Patient E., boy, 11 months. There are no specific findings of a life history. The child was observed by the neurologist at the community-based outpatient clinic due to the development delay (the boy can’t sit down and stand up). At the age of 8 months, the abdominal mass extending to the spinal canal was detected with ultrasound and CT scan. A biopsy of retroperitoneal tumor node was performed. NB was diagnosed. The patient was hospitalized in Dmitry Rogachev Federal Scientific Centre of Hematology, Oncology and Immunology for further examination and treatment. The neurological status at admission: psychomotor retardation, flail leg syndrome to 3 points, without significant dynamics in the last month. MRI revealed the retroperitoneal tumor on the right, extending to paravertebral soft tissue and the spinal canal (Th9—S2) (Fig. 1a). The diagnosis: Retroperitoneal NB extending to the spinal canal (Th9—S2), Stage III, MYCN-negative. Considering the stable neurological status, despite a huge size of the spinal cord tumor, it has been decided to refrain from neurosurgery.

After three cycles of chemotherapy according to NB-2004 protocol, there was a slight reduction in tumor size was observed (see Fig. 1b). This was accompanied by the increased strength in the legs to 3.5–4.0 points, and the boy began to walk hand in hand. The child was discharged for the dynamic observation at the community-based outpatient clinic. The follow-up period was 9 months.

Clinical case No. 2

Patient M., girl, 1 year and 2 months. Until the age of 1 year and 1 month, she was healthy. Then the child began to limp, there was a low-grade fever. The active movements in the legs disappeared completely within a week. Pediatrician and neurologist suspected a viral infection. She was hospitalized in the neurology department of the community-based clinic with flail leg syndrome. The examination (abdominal ultrasound and CT scan) revealed a tumor of the left retroperitoneal space with invasion into the spinal cord. She was hospitalized in Dmitry Rogachev Federal Scientific Centre of Hematology, Oncology and Immunology for further examination and treatment. There was flail leg syndrome to 0.5 points at admission. The pelvic organ functions were controlled. MRI revealed a retroperitoneal tumor, extending to the spinal canal on the left (Th10—L2), with the spinal cord compression (Fig. 2a, b).

Considering the rapid and dramatic increase in neurological symptoms, the osteoplastic laminotomy with resection of extradural spinal tumor (Th10—L2) was performed urgently. In the postoperative period, the increased strength in the legs was observed (see Fig. 2c).

Based on the results of the further examination, NB of the left retroperitoneal space, stage IV, with intraspinal extension (Th10—L2) and the spinal cord compression was diagnosed. The girl received a combined therapy according to NB-2004 protocol. The neurological status after 1.5 years: reduced strength in the legs to 4 points, more on the left, the pelvic organ functions were normal; walking with external support.

Clinical case No. 3

Patient K., girl, 1 month. On the 4th day after birth, the loss of movement in both legs was noted. The abdominal ultrasound revealed a retroperitoneal mass localized between the spine and left kidney. MRI revealed...
the extradural spinal cord tumor on the left (Th10—L4) with the paravertebral extension (Fig. 3a).

A biopsy of the tumor was performed. Histological diagnosis: NB. The patient was hospitalized in Dmitry Rogachev Federal Scientific Centre of Hematology, Oncology and Immunology for further examination and treatment. The neurological status at admission: lower paraplegia; lower extremity tendon reflexes are absent; incompletely closed anus, urinary leak.

After a comprehensive examination, retroperitoneal NB of the left retroperitoneal space, stage III was diagnosed. Considering the neurological disorders since the birth, their duration and severity, it has been decided to refrain from neurosurgery. The chemotherapy was

Fig. 1. Patient E.
a — spine MRI at admission. T1WI: in the spinal canal (Th9—S2) is visualized NB nodule, actively accumulating contrast agent. Thickening and antedisplacement of the spinal cord at the level Th8 and a marked compression of the lower spinal cord by the tumor. The cauda equine is not visualized; b — a reduction of the tumor size by 25% compared with the baseline value. The cauda equine is visualized.

Fig. 2. Patient M.
a, b — MRI at admission. On MRI images (sagittal and axial projections): a huge tumor, localized in the retroperitoneal space and paravertebrally (Th8—L5). At the level of Th10—L2: NB extends through the intervertebral foramina to the spinal cord on the left. At the level of Th11—L1: tumor mass shifts to the right and compresses the dural sac and spinal cord, occupying up to 70% of the spinal canal diameter; c — MRI after surgery. Almost complete resection of the spinal cord tumor. Expansion of the dural sac.
performed according to NB-2004 protocol. The control MRI revealed a reduction of tumor size: intraspinal component by 35%, paravertebral component by 31% (Fig. 3b). The strength in the legs corresponds to paraplegia, but the child has normal urination and anal reflex. There was a stable disease at last examination. The follow-up period was 17 months.

We presented three observations, where the tumor with a significant intravertebral extension and the spinal cord compression has different clinical manifestations, from mild paraparesis (first clinical case) to congenital paraplegia (third clinical case). The chemotherapy was conducted, if neurological status was stable (consistently good or consistently poor). Due to the progression of neurological deficit (second clinical case), prompt surgical decompression of the spinal cord was performed with a positive outcome.

Discussion

Despite the apparent benefits of primary surgical decompression of the spinal cord, the modern experience in the treatment of children with intraspinal tumor extension does not reveal its advantages over chemotherapy. In the literature [5, 8—12], there are a series of observations, published since 2000, which compared the outcomes and complications of surgical and chemotherapeutic decompression (radiation therapy is currently not used in early treatment period) (Table).

The table shows a small number of patients included in the studies; the most representative German overview includes 99 patients for 20 years [10]. No study has shown the advantages of primary surgical decompression over chemotherapy. Conversely, both methods give approximately similar functional results. Neurological disorders of various nature and severity persist in the majority of patients (60—70%) in the long-term period, regardless of primary treatment. There is also no difference in the survival rates in patients who initially underwent surgery or chemotherapy.

On the other hand, a higher rate of spinal deformities after surgical tumor resection was observed in a series of studies [5, 8, 9, 11]. The modern intervention technique (osteoplastic laminotomy and neurophysiological monitoring) probably will reduce the incidence of these complications.

The need for surgery in the reported cases is still being discussed in the literature [13]. The spinal cord tumor on MRI, both asymptomatic and with signs of spinal cord compression, is not an absolute indication for surgical resection. If the patient's neurological status is stable (consistently good or consistently poor), the resection of the intraspinal tumor is not appropriate [5, 11, 12]. This issue should be discussed in conjunction with the pediatric oncologist, and the method of choice may be chemotherapy. The absolute indication for the surgical intervention is a rapid (within a few days or weeks) growth of the neurological deficit. In this case, the factor of decompression speed is important. The
surgery is also indicated if it is known that this type of tumor does not require chemotherapy, and the only therapeutic option is surgical intervention according to the treatment protocol. [12] The surgery may be considered as the first option when a tumor sample is necessary to determine the histological type, and the surgery should still be performed as an alternative to laparotomy or thoracotomy. We are also faced with a problem of increased neurological deficit after chemotherapy due to edema of the tumor tissue, and the improvement of neurological status could be achieved only after surgical resection of the spinal cord NB.

Intracranial metastases of neuroblastoma

NB often metastasizes to the cranial bones and orbit (Fig. 4, our own observation). The patients with orbital metastases demonstrated such symptoms, as the periorbital ecchymoses and proptosis. The specific surgical treatment is not required. The standard complex therapy is conducted in accordance with the risk group [1, 2, 14, 15].

Primary CNS metastases of NB have almost never occurred at the diagnosis. The tumor nodules are detected in the brain and spinal cord, or meningeal membranes in 5—7% of patients during or after the main course of treatment (Fig. 5). The prognosis for the most patients is unfavorable, despite the intensive therapy including surgery, chemotherapy and radiation therapy [14—16].

Opsoclonus-myoclonus syndrome

Opsoclonus-myoclonus (OMC) in children with NB refers to a paraneoplastic syndrome, and formally, is not related to neurosurgery. It is manifested a specific triad: opsoclonus (eye twitching similar to a horizontal nystagmus), myoclonus (twitching of the limbs, trunk and facial muscles) and ataxia. Opsoclonus-myoclonus syndrome occurs in 2—4% of NB patients. On the other

<table>
<thead>
<tr>
<th>Author, year publications</th>
<th>Country, years</th>
<th>Number of patients</th>
<th>Surgery/CT/RT</th>
<th>Complications</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Katzenstein, 2001 [9]</td>
<td>USA, 1990-1998</td>
<td>83 (43)</td>
<td>Surgery — 5 CT — 19 CT + Surgery — 17</td>
<td>Spinal deformity in 7 of 8 patients undergoing surgery</td>
<td>There are no differences in outcome between treatments</td>
</tr>
</tbody>
</table>

Footnote. 1 — the total number of patients (the number of patients with the neurological deficit). CT — chemotherapy; RT — radiotherapy.

Fig. 4. Brain MRI. A huge NB metastasis to the parietal bone with a massive intra- and extracranial dissemination. Due to the extensive metastatic dissemination (cranial bones, liver, bone marrow, lymph nodes), an attempt to remove this metastasis was not undertaken.
The metastasis was removed. The patient received a course of second-line polychemotherapy. The follow-up period is 26 months from the date of surgical intervention.

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This work presents the clinical observations of pediatric patients with neuroblastoma and signs of CNS involvement (the brain and spinal cord). Based on these examples, the authors analyze the current state of this issue in terms of the rationale for neurosurgery.

The modern approach to the treatment of neuroblastoma (high-grade embryonal tumor) reflects the general oncology trends: histological diagnosis, molecular-genetic typing, clinical staging and the standard combined therapy. In most cases, surgical intervention is a therapeutic option for a second and third stage. Historically, the primary treatment of patients with neuroblastoma and signs of spinal cord compression were performed by neurosurgeons, which included urgent decompression of the spinal cord by removal of the tumor from the spinal canal. The most significant adverse event of this therapeutic approach is a relatively high incidence of the long-term spinal deformities. Some current studies also demonstrate a positive outcome of chemotherapy as “neoadjuvant” therapy in terms of spinal decompression by a rapid decrease in tumor volume. The authors clearly illustrate this conception by their clinical cases.

In my opinion, the work is essential for two reasons. First, the authors for the first time in the Russian neurosurgical literature discuss inappropriate compulsory resection of primary spinal cord neuroblastoma. Second, perhaps more important, the authors show that any standard treatment in the actual clinical setting is not absolute and, despite the success of oncology, patients with rapidly progressive reversible neurological deficit are candidates for urgent neurosurgery.

Yu. Kushel (Moscow, Russia)
The mean life span documented in 2012 was 70 years. According to WHO estimates, the world population aged 60 years and older amounted to 600 million people in 2000, which was almost 3 times higher than the population of this age group in 1950 (205 million people). In 2009, the population exceeded 737 millions; by 2050, it will amount to more than 2 billion people, again tripling in 50 years.

Today, the trend is that people even in old age seek to keep a habitual active lifestyle: pursue professional activities, travel, and play sports. One of the obstacles on this way is disabling pathology of the spine caused by a degenerative-dystrophic process that can lead to spinal deformity due to asymmetric degeneration of the intervertebral discs and facet joints [2].

The spinal deformity is a common problem among the elderly, and its prevalence grows as the mean age of the population increases. According to various authors [3, 4], the rate of spinal deformities varies from 2 to 68% in the population of people older than 60 years.

The main cause of back pain in elderly patients with spinal deformity is sagittal imbalance. The sagittal imbalance problem should be resolved with allowance for the spinopelvic relationships [5, 6] that are evaluated from full height X-ray images (Fig. 1).

The pelvic incidence (PI) is the angle between a line connecting the midpoint of the S1 superior end plate and the femoral head center (or the midpoint of a line between centers of the femoral heads) and a line perpendicular to the center of the S1 superior end plate.

The pelvic tilt (PT) is the angle between a line connecting the midpoint of the S1 superior end plate and the femoral head center (or the midpoint of a line between centers of the femoral heads) and a vertical line.
The sacral slope (SS) is the angle between a line parallel to the S1 superior end plate and a horizontal line. The lumbar lordosis (LL) is the Cobb angle between the T12 and S1 superior end plates. The thoracic kyphosis (TK) is the Cobb angle between the T5 and T12 superior end plates. The sagittal vertical axis (SVA) is the C7 plumb line. The distance from the axis to the posterosuperior corner of the S1 vertebra is the sagittal imbalance value.

A study by F. Schwab et al. [7] demonstrated a correlation between pain intensity on the visual analogue scale (VAS) and the degree of spinal deformity. The greater the curvature is, the more intense the pain is. Later, this topic was developed: the authors concluded that the quality of life in spinal deformity patients is characterized by lower values of all 8 scores of the SF-36 scale compared to the averaged scores for the US population older than 55 years [8]. Baldus S. et al. [9, 10] obtained convincing evidence of a decrease in the activity and quality of life (according to the SRS-24 questionnaire for assessing quality of life and patient’s satisfaction with the results of surgical correction) in patients with idiopathic scoliosis and scoliosis de novo (degenerative scoliosis). In this case, the older the patient groups are, the more pronounced the differences are. When separated by gender, the averaged results were poorer than in males. J. Mac-Thiong et al. [11] also related the quality of life to a change in the sagittal spinal balance. A C7 plumb line deviation relative to the posterior corner of the S1 superior end plate on full height teleroentgenograms and/or a displacement of the center of gravity in a posturography test by 6 cm are factors of disability in patients according to the Oswestry Disability Index (ODI). The orthopedic component is often ignored in treatment of elderly patients with spinal deformities, while rebalancing of the spine is an important requirement for a favorable outcome of the treatment.

Material and Methods

We prospectively studied 58 patients treated at the Vreden Russian Research Institute of Traumatology and Orthopedics in the period from 2007 to 2010. The study included patients aged over 60 years with spinal deformity (sagittal modifiers of grade 2(+) and higher according to the SRS-Schwab classification [12]), radicular syndromes, and back pain (Table 1).

All patients were divided into two groups, depending on the type of applied surgery: group 1 consisted of 28 patients who underwent medial foraminotomy only at levels where compression of neural structures was identified; group 2 included 30 patients who underwent decompressive surgery combined with restoration of sagittal and frontal balances. To correct the spinal balance in the 2nd group, multilevel Smith-Petersen osteotomy (resection of the articular and, partially, spinous processes in the spinal motion segment (SMS)) for small deformities and pedicle subtraction osteotomy (PSO) for pronounced deformities were used. Osteotomy was combined with fixation using pedicle systems. The length of fixation depended on the deformity length and severity of spinal imbalance. The standard option for sagittal balance correction was fixation of the whole lumbar lordosis. However, if a neutral vertebra (a vertebra lacking rotation) was located above T10, we used extended instrumentation from the lumbosacral segment to the T3—T4 level. Arthrodesis of the L5—S1 segment combined with fixation to the ilium bones was performed for degenerative changes in the L5—S1 segment, or for long fixation (from the lumbosacral to upper thoracic segment), or for PT of over 30°.

Before surgery, all patients were examined using a general algorithm that included general clinical and neurological examinations and an X-ray examination with measuring spinal deformity using the Cobb method,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68.7±5.7</td>
<td>65.4±5.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.8±5.7</td>
<td>32.9±5.7</td>
</tr>
<tr>
<td>Females</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Males</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Scoliosis, °</td>
<td>31.2±6.5</td>
<td>38.7±8.2</td>
</tr>
<tr>
<td>Kyphosis, °</td>
<td>64.1±7.6</td>
<td>62.3±11.2</td>
</tr>
<tr>
<td>Lordosis, °</td>
<td>−16.2±14.8</td>
<td>−12.4±16.5</td>
</tr>
<tr>
<td>PT, °</td>
<td>27.4±11.3</td>
<td>29.8±14.1</td>
</tr>
<tr>
<td>SS, °</td>
<td>31.0±8.4</td>
<td>18.8±12.3</td>
</tr>
<tr>
<td>PI, °</td>
<td>58.3±9.2</td>
<td>48.6±11.8</td>
</tr>
<tr>
<td>SVA, mm</td>
<td>7.4±2.5</td>
<td>8.7±3.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>Decompression</td>
<td>Decompression + correction + fixation</td>
</tr>
</tbody>
</table>

Fig. 1. A diagram of the sagittal balance and spinopelvic relationships.
with assessing the spinopelvic relationships and sagittal imbalance values on teleroentgenogramms.

Treatment outcomes were evaluated using VAS, ODI, and SRS-24 scores. The patients were surveyed through all parameters before surgery. Evaluation using VAS was performed 10 days after surgery. Further, evaluation using the three scales was performed at 3 and 6 months, 1, 2, and 5 years. Patients in group 2 underwent repeated teleroentgenography after surgery to evaluate the degree of deformity correction.

In statistical data processing, we used the Student t-test for independent groups. A value of \( p < 0.05 \) was considered statistically significant.

### Results

The mean age of patients was 67 years. Overweight was present in 81% of them. Before surgery, the groups had no differences, except the indicators (Fig. 1) of pelvic incidence (PI) and sacral slope (SS), which were lower in group 2; however, the differences were not statistically significant (\( p > 0.05 \)). After surgery, satisfactory indicators of the sagittal balance (the difference between LL and PI within 10°, SVA ≤ 4 cm, and PI ≤ 20°) were observed in 72% of the patients.

Changes in the quality of life indicators before and after surgery are shown in Table 2.

Table 2. Comparison of quality of life indicators between groups

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group 1</th>
<th>Group 2</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS, score</td>
<td>7.6±1.2</td>
<td>7.8±1.8</td>
<td>0.968</td>
</tr>
<tr>
<td>ODI, %</td>
<td>77.4±14.1</td>
<td>78.1±15.2</td>
<td>0.502</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>36.8±8.12</td>
<td>37.7±9.2</td>
<td>0.537</td>
</tr>
<tr>
<td>10 days after surgery</td>
<td>3.7±2.4</td>
<td>4.3±2.1</td>
<td>0.168</td>
</tr>
<tr>
<td>VAS, score</td>
<td>2.8±3.3</td>
<td>4.1±2.7</td>
<td>0.964</td>
</tr>
<tr>
<td>ODI, %</td>
<td>41.8±11.4</td>
<td>52.1±12.7</td>
<td>0.031*</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>71.6±9.4</td>
<td>74.2±11.7</td>
<td>0.215</td>
</tr>
<tr>
<td>3 months after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS, score</td>
<td>2.7±0.8</td>
<td>2.9±1.2</td>
<td>0.759</td>
</tr>
<tr>
<td>ODI, %</td>
<td>34.3±8.8</td>
<td>37.5±10.4</td>
<td>0.605</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>82.3±13.1</td>
<td>80.4±4.8</td>
<td>0.848</td>
</tr>
<tr>
<td>6 months after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS, score</td>
<td>3.4±2.3</td>
<td>2.6±1.9</td>
<td>0.105</td>
</tr>
<tr>
<td>ODI, %</td>
<td>39.2±10</td>
<td>32.6±9.2</td>
<td>0.201</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>74.7±6.7</td>
<td>72.6±12.3</td>
<td>0.76</td>
</tr>
<tr>
<td>1 year after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS, score</td>
<td>5.9±2.1</td>
<td>3.1±1.4</td>
<td>0.043*</td>
</tr>
<tr>
<td>ODI, %</td>
<td>41.1±9.6</td>
<td>33.2±10.1</td>
<td>0.098</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>45.1±7.8</td>
<td>70.5±9.2</td>
<td>0.012*</td>
</tr>
<tr>
<td>2 years after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS, score</td>
<td>7.1±2.2</td>
<td>2.9±3.1</td>
<td>0.045*</td>
</tr>
<tr>
<td>ODI, %</td>
<td>63.1±12.1</td>
<td>28.9±7.9</td>
<td>0.009*</td>
</tr>
<tr>
<td>SRS-24, score</td>
<td>50.2±8.7</td>
<td>70.9±9.4</td>
<td>0.027*</td>
</tr>
<tr>
<td>5 years after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnote. * — statistically significant difference.

Improvement in pain occurred in both groups and was scored 3.7±2.4 in the 1st group and 4.3±2.1 in the 2nd group, with no statistical difference between the groups (\( p = 0.168 \)). No assessment using ODI and SRS-24 scales was performed after surgery.

Three months after surgery, the result in group 1 according to VAS (2.8±3.3) and ODI (41.8±11.4%) were better than those in group 2 (4.1±2.7) and (52.1±12.7%), respectively, with the ODI differences being statistically significant (\( p = 0.031 \)). After 3 months, there was no statistically significant difference between the results on the SRS-24 scale. On an examination after 6 months, both groups had already comparable indicators of the quality of life. However, after one year, negative changes were observed in the 1st group compared to the examination at 6 months: 3.4±2.3 (VAS), 39.2±10% (ODI), and 74.7±6.7 (SRS-24). The mean values in group 1 one year after surgery were worse than those in group 2. After 2 years, there were significant differences in pain between the 1st and 2nd groups: 5.9±2.1 vs. 3.1±1.4 (VAS) and 45.1±7.8 vs. 70.5±9.2 (SRS-24). After 5 years, there were statistically significant differences in all evaluated parameters between the two groups.

### Discussion

At the current stage of spine surgery development, treatment results are largely assessed by patients...
themselves. A subjective patient’s perception of pain and neurological deficit, which depends on the adaptation to disturbance of the usual lifestyle behavior, becomes significant. Therefore, evaluation of surgical treatment outcomes has been shifted in favor of quality of life questionnaires [13—15].

Adult scoliosis deformity of over 15° is known to be associated with significant changes in the sagittal balance. Changes in the sagittal plane correlate with pain and the degree of disability, while the value of deformity in the frontal plane insignificantly affects the pain sensation [16]. The threshold values of a change in the sagittal balance for a severe disability degree (ODI> 40) are as follows: PT is 22° or more; SVA is 47 mm or more; the difference between PI and LL is 11° or more [17]. K. Fu et al. [18] found that the choice in favor of surgical treatment in patients over 60 years was related to sagittal imbalance and imbalance-associated disability.

In the present study, we analyzed how spinal deformity and instability affect the quality of life in patients older than 60 years who underwent two different types of surgery. Before surgery, the patients had comparable scores by VAS, ODI, and SRS-24. Persistent performance impairment was observed in both groups, despite the evidence that even poor preoperative indicators do not affect the treatment outcome [19]. In the postoperative period, all patients reported a decrease in pain.

Isolated decompressive surgery without deformity correction in the 1st group had poorer outcomes in the late period compared to those in patients with spinal balance correction in the 2nd group. Uncorrected deformity adversely affects outcomes in the postoperative period [20]. On the other hand, K. Fujii et al. [21] noted that isolated decompression of a moderately deformed lumbar spine resulted in improved indicators of spinal balance. Other researchers [22, 23] showed that there were no differences in 2-year outcomes, regardless of performing deformity correction and stabilization. According to P. Mummaneni et al. [24], decompressive surgery without spinal balance correction can be indicated only for the following patients: non-rigid deformity; the difference between LL and PI <10°; SVA <6 cm; PI <25°; minimal laterolisthesis (<6 mm); scoliosis <20°; no hyperkyphosis (> 40°). In our study, patients in group 1 experienced pain relief and improved quality of life after surgery, which lasted about one year. Later, progressive deterioration in all indicators occurred in this group (Fig. 2—4).

According to our findings, isolated decompression leads to progressive SMS instability and decompensated clinical symptoms in the form of pain recurrence in the
long-term (5 years) period, which is consistent with the data of international studies. On the basis of a meta-analysis of 49 papers and treatment outcomes in 3,299 patients, S. Yadla et al. [25] concluded that surgery for spinal deformity correction significantly improves the quality of life in patients.

An outcome of surgical treatment of the spine in terms of the relationship among improvement in the quality of life of patients after surgery, the rate of complications, and the degree of surgical aggressiveness still remains an unresolved issue. The number of postoperative complications grows as the degree of instrumentation increases. In US hospitals, the rate of multilevel fixation in patients older than 65 years increased 15 fold in the period from 2002 to 2007. In this case, the number of different serious complications more than doubled. The readmission rate increased from 7.8 to 13%. In this situation, the cost of patient treatment more than tripled [26]. However, despite potential risks, surgery for deformity correction and sagittal balance restoration has a social value associated with improvement in the quality of life, restoration of functional autonomy, and a reduction in expenses associated with financing of disabled people [27].

**Conclusion**

Evaluation of the quality of life in the long-term period after surgery is important for defining the indications for surgical treatment. A surgical option for treatment of the degenerative scoliosis patient should be chosen with allowance for a potential outcome of the surgery. Isolated decompressive surgery provides good short-term outcomes, followed by deterioration in the condition. Decompression combined with spine stabilization and correction of sagittal and frontal imbalances is more traumatic, but more efficient. Restoration of spinal balance is an important requirement for a positive outcome of surgical treatment in the long-term period.

Authors declare no conflict of interest.

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Commentary

The topicality of spinal deformity treatment is indubitable because of a high prevalence of various forms of the disease in the population, especially in elderly patients. In addition, the dynamically developing area of medicine in general and surgery of the spine in particular, which allows professionals to conduct large-scale studies in large groups of patients, results in annually growing interest of professionals to this issue.

The last decade has been characterized by an active search for the patterns of spinal deformity development and ways to prevent it. Of great importance in the search for these patterns is studying the pathogenetic role of spinopelvic and sagittal balance parameters in the development of lumbar spine degenerative changes that in turn are obviously related to age. A number of studies in patients with degenerative stenosis of the lumbar spinal canal confirmed a relationship between severity of degenerative changes as well as age and values of spinopelvic and sagittal balance parameters. In addition, the quality of life in elderly patients in the presence of these changes is affected much greater than that in younger patients. This fact, of course, confirms the topicality of the present work that evaluates the quality of life in elderly patients with spinal deformity after surgery.

In the present work, the authors performed a prospective analysis of 58 patients with spinal deformity who underwent surgical treatment at the Vreden Institute. It is worth noting a structured plan for selection, examination, and analysis (based on a pain scale and questionnaires) of patients included in the study. The patients were divided into two groups according to the surgery option. In one group, patients underwent decompressive surgeries aimed at solving local treatment tasks, without active restoration of sagittal balance. In another group, patients underwent radical surgery for decompression of neural structures and restoration of frontal and sagittal spinal balances. To evaluate the treatment outcomes (in particular, long-term outcomes, which are of the greatest interest), the authors chose and used conventional international scales and questionnaires that underlie modern trends in assessment of the efficacy of treatment and quality of life in patients undergoing surgery. This is especially true in the field of developing the principles of surgical care to elderly patients with degenerative changes of the spine.

It is important to understand that prevention of static impairments and sagittal imbalance in patients in the postoperative period is now one of the priorities of practical...
medicine. Minimization of errors associated with a technical aspect of surgery is one of the most important tasks, the successful solution of which positively affects the outcome.

An equally important aspect of the present study is, as marked by the authors, the trend, which is generally accepted in the international surgical community, to minimize the traumatic effects of surgery and its correlation with long-term outcomes of surgical treatment. Therefore, the issue of a preferred extent of surgical radicalness still remains open.

In this context, of significant scientific and clinical interest are the findings indicating a better outcome of treatment in the early postoperative period in patients with pronounced deformity after less traumatic surgery compared to patients after radical surgery. Changes in the assessment of outcomes in the long-term period are totally opposite. However, the choice of a less traumatic surgical technique seems to be justified in the case of moderate deformity. The obtained results correlate with the literature data, which confirms the scientific significance of the study.

In addition, it seems extremely interesting to evaluate the quality of life and social adaptation in patients older than 60 years after surgery who have developed changes. However, a more definite picture requires additional detailed investigation using optimal evaluation tools.

Therefore, the problem of choosing a surgery option for patients with spinal deformity is now related to the expected assessment of life quality of patients in the long-term period and the assessment of severity of degenerative and scoliotic spinal changes. Furthermore, particular attention should be paid to frontal and sagittal balance changes that directly affect the clinical manifestations and course of degenerative disease in elderly and senile patients after various surgical treatments. It should be recognized that the issue of choosing a surgery option for patients with degenerative scoliosis remains open and requires large-scale studies. Future results will be helpful in developing a surgical treatment approach for patients with various forms of degenerative and scoliotic spinal changes.

The presented material enables defining the purpose and objectives of upcoming studies that will have a significant effect on improving the quality of surgical treatment.

N.A. Konovalov, D.S. Asyutin (Moscow, Russia)
The development of effective algorithms for management of tethered cord syndrome (TCS) is an issue of major health concern in pediatric neurosurgery [1—4]. TCS is characterized by presence of sensory, motor, and trophic disorders of the lower extremities, musculoskeletal deformities, pelvic and other disorders of different severity resulting from immobilization and caudal spinal cord stretching during rapid growth of a child with spinal dysraphia and also due to processes of scar and adhesion formation, inflammatory or neoplastic processes [5]. Only one study contains data on several patients with “classical” TCS caused by filum terminale abnormalities (inelastic, thickened, shortened filum terminale, lipoma of the filum terminale), the results of which suggest that such patients comprise no more than 0.1% of the population [6]. The incidence of neural tube defects with stretching and deformation of the terminal spinal cord comprises at least 1 case per 1,000 newborns [7]. Due to substantial differences in the etiology and mechanisms of TCS, verification of the factors that influence the outcome of surgery should be recognized as a reasonable matter. In particular, identification of structural changes in spinal tracts is obviously necessary.

In order to clarify the indications for surgery and development of effective algorithms for surgical treatment of TCS, we have compared data on spinal 3T MRI tractography with data collected during clinical and neurophysiological examination of children with filament terminale abnormalities and caudal lipomas, as well as patients with secondary spinal cord tethering caused by scar formation after lumbosacral myelomeningocele repair.

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reduction factor was 2.0. Sequence parameters — TE/TR 60/6247, slice thickness — 2, slice distance — 0, number of slices and imaging field varied depending on the child’s growth. Repetition factor was 2 and the maximum b-factor was 800.

Postprocessing analysis was carried out using the Extended mr workspace station (version 2.6.3.4) with Fibetrac software package and included automatic generation of fractional anisotropy (FA) maps in three orthogonal planes and construction of tracts. The level of an interruption of the tract (LIT) on tractograms was determined and the average numerical values of FA proximal to LIT were evaluated. In children under 5 years the research was performed under medical sedation and analgesia. Correlation of FA with age of a child was assessed by a regression and correlation analysis (Pearson’s correlation analysis). Kruskal-Wallis test (H-test) was used to determine dependence of FA on ML and LIT. Prognostic test was conducted to determine sensitivity. SPSS 22 software package for Windows was used for statistical analysis.

Results

Based on the results of clinical introscopic comparison, two groups of patients were identified.

The first group included 10 children with filum terminale abnormalities and caudal lipomas (Table 1). These patients typically presented with moderate sensory and motor disorders, which did not correspond to certain myotomes and dermatomes, as well as equal suppression of tendon reflexes, dysregulation of pelvic functions (paroxysmal incontinence, retention), progressive scoliotic spinal deformity, shortening of one of the lower extremities followed by a claw-toe deformity (shortened foot length, a high arch). The development of clinical symptoms was associated with periods of accelerated growth of children. According to introscopy data, despite the low location and features of a tethered spinal cord, changes in spinal tracts in this group of patients have not been revealed and fractional anisotropy indices ranged within 0.373—0.556.

Correlation analysis established that FA depended on age in this group (r=0.47), but this relationship was not statistically significant (p=0.166; F=2.32, 1–β=1.35%), which may be due to the small number of observations.

All patients of this group showed regression of clinical manifestations of TCS after operation on tethered spinal cord release. An increase in the amplitude and a decrease in the latency of MEPs from lower limb muscles were also identified.

Clinical example 1

A girl aged 8 years. The patient presented with weakness of the lower leg and foot flexors (ML S), more on the right, scoliotic deformity of the spine I grade, and occasional urinary incontinence. During examination, area of hypertrichosis in the lumbosacral region attracted our attention (Fig. 1a). Spine radiographs showed signs of spina bifida at L4—S1 vertebral arches (Fig. 1b). MRI examination established deepening of lumbar lordosis, tethered spinal cord at the L4—L5 vertebral level (Fig. 1c). MRI tractography identified spinal tracts along its entire length (Fig. 1d). Indicators of FA at L2 — 0.310 and at L3 — 0.469. When recording MEPs from lower limb muscles motor responses of the following latency and amplitude were received: from mm tibialis ant., peroneus dex. (1) latency — 24.8 ms, amplitude — 0.191 mV, from mm tibialis ant., peroneus sin. (2) latency — 20.2 ms, amplitude — 0.133 mV (Fig. 1e — 1.2). Thickened, stretched filum terminale infiltrated by adipose tissue was detected intraoperatively (Fig. 1f).

After identification by electro-stimulation (current 10 mA, motor responses are absent) (Fig. 2a, b) filum terminale was incised at a distance of 10 mm from the conus causing marked cranial migration of the conus (Fig. 2c, d). Positive dynamics was observed during examination in the early postoperative period: regression of pelvic disorders, increase in muscle strength in the lower extremities. FA level was greater than 0.5 (Fig. 2e) on control MRI with MRI-tractography. Analysis of MEPs in dynamics established a decrease in the latency and an increase in the amplitude of the responses on the right: mm tibialis ant., peroneus dex. (1), latency — 18.1 ms, amplitude — 1.07 mV (Fig. 2f — 1).

The second group consisted of 11 children, patients with secondary spinal cord tethering caused by scar formation after lumbosacral myelomeningocele repair. Along with characteristic MR-signs of spinal tract injury at the level of myelomeningocele repair we detected coarse congenital motor deficit (flaccid paralysis) followed by loss of all kinds of sensitivity distal to LIT, trophic disorders (muscle hypertrophy), marked deformity of the spine and lower extremities (kyphoscoliosis, equinovarus deformity of the feet), as well as urinary and fecal incontinence. ML in these children corresponded to LIT, and FA indices above LIT were slightly reduced versus examination data of the first group of patients (Table 2).

Table 2. Patients with filum terminale abnormalities and caudal lipomas

<table>
<thead>
<tr>
<th>Age, years</th>
<th>ML</th>
<th>LIT</th>
<th>FA (N 0.2—0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S</td>
<td>L5–S1</td>
<td>0.373</td>
</tr>
<tr>
<td>3</td>
<td>S</td>
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</tr>
<tr>
<td>5</td>
<td>S</td>
<td>L5</td>
<td>0.388</td>
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<tr>
<td>7</td>
<td>S</td>
<td>L5</td>
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</tr>
<tr>
<td>8</td>
<td>S</td>
<td>L5</td>
<td>0.389</td>
</tr>
<tr>
<td>8</td>
<td>S</td>
<td>S1–S2</td>
<td>0.485</td>
</tr>
<tr>
<td>9</td>
<td>S</td>
<td>L5–S1</td>
<td>0.448</td>
</tr>
<tr>
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<td>L5–S1</td>
<td>0.407</td>
</tr>
<tr>
<td>14</td>
<td>S</td>
<td>L5–S1</td>
<td>0.487</td>
</tr>
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</table>

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Correlation analysis identified no correlation of FA to the age of children ($r=0.08; p=0.82$). Correlation of FA to ML ($H=3.15; p=0.37$) and to LIT ($H=4.1; p=0.54$) was neither identified.

Surgical treatment aimed at tethered spinal cord release did not change ML in these patients, despite some motor and sensory improvements.

**Clinical example 2**

A girl aged 3 years. Based on the medical record, lumbosacral myelomeningocele repair was urgently performed at birth due to liquorhea. The clinical presentation at admission included lower flaccid paraparesis (ML L3—L4), dermatomal anesthesia from level L3—L4, urinary and fecal incontinence. MRI (Fig. 3a) showed spina bifida at L3—S2 vertebral arches, spinal cord extends to the caudal vertebral body L3, where it represents as a frontal plate shifted to the posterior wall of the dural sac and is anchored to it. There are spinal cord roots running transversely along the posterior folium of the dura mater. On tractograms (Fig. 3b) tracts can be traced to the area of cord anchoring to the posterior folium of the dura mater at the L3—L4 level, the FA level is 0.389—0.419. In the study of MEPs from lower limb muscle motor responses are registered only from \textit{m. rectus femoris} (Fig. 3d). Coarse scarring of the spinal cord and meninges were revealed intraoperatively at the level of myelomeningocele repair (Fig. 3c). After myelomeningocele repair and tethering release motor responses from the muscles of the lower extremities during stimulation of the roots (Fig. 3e) (current — 10 mA) were not obtained (Fig. 3f).

In the postoperative period, improvement in sensitivity and an increase in muscle strength in the lower extremities were observed, but ML remained the same. Control MRI with MRI tractography showed that the caudal spinal cord migrates in a cranial fashion, the roots become ascending and the length of tracts and FA indices were without significant dynamics (Fig. 4).

**Discussion**

Identification of the indications to perform tethered cord release in patients with TCS is based on the concept of reversibility of a neurological deficit and improving the prognosis of the disease during restoring spinal mobility by surgical removal of the factors that cause deformation and stretch of the caudal spinal cord and roots of the cauda equina [5]. In our series of observations the condition after surgery was stabilized in all cases and clinical manifestations regressed in a significant proportion of patients. Because TCS is considered a dynamic condition wherein neurological deficit, as a rule, progresses, stabilization of the condition can be considered a positive treatment outcome [1—3].

Revealing the factors that determine the reversibility of clinical manifestations during TCS appears important. These factors can be determined by both injury of the...
Table 2. Patients with secondary spinal cord tethering caused by scar formation after lumbosacral myelomeningocele repair

<table>
<thead>
<tr>
<th>Age, years</th>
<th>ML</th>
<th>LIT</th>
<th>FA (N 0.2—0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>Th</td>
<td>Th</td>
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</tr>
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<td>1.5</td>
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<td>2</td>
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<td>L4—L5</td>
<td>0.361</td>
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<td>L3—L4</td>
<td>L3—L4</td>
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</tr>
<tr>
<td>6</td>
<td>L4—L5</td>
<td>L5</td>
<td>0.405</td>
</tr>
<tr>
<td>6</td>
<td>L4—L5</td>
<td>L4—L5</td>
<td>0.399</td>
</tr>
<tr>
<td>6</td>
<td>L3—L4</td>
<td>L3—L4</td>
<td>0.386</td>
</tr>
<tr>
<td>6</td>
<td>L3—L4</td>
<td>L3—L4</td>
<td>0.391</td>
</tr>
<tr>
<td>12</td>
<td>L4—L5</td>
<td>L4</td>
<td>0.390</td>
</tr>
</tbody>
</table>

Fig. 2. a — monopolar electro-stimulation of filum terminale (current — 10 mA); b — motor responses from lower limb muscles are not recorded; c — incision of filum terminale; d — migration of segments of incised filum terminale; e — MRI with MRI tractography after surgery; f — postoperative image of evoked motor potentials from mm tibialis ant., peroneus dex.

Experimental studies of a number of authors have demonstrated a high degree of compensation in the long tracts (dorsal columns) during their stretch and ischemia [22, 23]. It was found that deterioration of the tract function of the ventral white matter strips of pigs occurred when the cord strips were stretched to a point when action potentials completely abolished, which corresponds to a two-time elongation of the cords [24]. In experiments with cats, whose caudal spinal cords were stretched, under stimulation of dorsal sacral roots and directing excitation from the anterior roots, interneuron potentials of cord segments declined their amplitude and increased latency [5].

The data of this study make it possible to consider TCS a pathological condition caused by stretch and is characterized by impaired cellular metabolism and conductive function of neurons of the gray matter. Based on that approximately 97% of gray matter in the caudal spinal cord represent interneurons of the propriospinal gray matter of the caudal segments and pathology of the spinal tracts. Traditionally, instrumental diagnostics of pathology of spinal tract system includes only the analysis of sensory and motor evoked potentials, but the final verification of the nature and prognosis of the disease requires the determination of the structural and functional organization of a pathological process as a whole. Modern neuroimaging techniques allow detection of structural changes in the spinal cord to differentiate pathology of gray matter and tract system. Diffusion-weighted MRI imaging mode is believed to allow one to receive data on flow of water molecules in tissues [10]. Based on that unidirectional flow of water molecules in the central nervous system is caused primarily by the presence of axonal membranes, 3D images generated during spinal diffusion-weighted MRI tractography, with a certain degree of conditionality, are regarded as the white matter tracts of the spinal cord [11—15]. The decrease of FA, which characterizes the degree of unidirectional diffusion of water molecules, is considered at present one of the signs of injury to spinal tracts in various pathological conditions [16—18]. This parameter is believed to be 0.2—0.5 for the caudal spinal cord in the norm [13, 16]. There is little experience in the use of MRI tractography during TCS in adults [19]. We have also presented the results of MRI tractography in children with consequences after lumbosacral myelomeningocele repair [20]. It is believed that clinical manifestations of TCS are formed as a result of spinal cord stretch, which has a negative impact on circulation and cellular metabolism [5]. It is known that axons of neurons due to their viscoelastic properties exhibit high tolerance to dynamic stretch injury [21].

Based on that approximately 97% of gray matter in the caudal spinal cord represent interneurons of the propriospinal...
system, giving rise to more than 60% of white matter fibers at this level [25—27], there is reason to believe that the development of TCS is also associated with injury of short propriospinal fibers which, due to their relatively shorter length, are more likely to suffer from stretching. Their excessive stretch can result in conductive violations or irreversible changes that lead to degeneration of nerve fibers. This hypothesis is indirectly confirmed by clinical signs of violation of the integrative function of the propriospinal system of the caudal spinal cord [25] in patients of the first group, as well as the loss of functions of cord segments distal to LIT in patients of the second group.

Sharp total interruption of tracts on MRT tractograms in these patients is likely to be caused by a sudden critical decrease in FA. The latter may be caused by injury of the propriospinal system tracts of the caudal spinal cord. A typical neuroimaging feature in this case is the lack of MRI tractography signs of retrograde degeneration of the long tracts of the spinal cord proximal to LIT [28, 29]. The dependence of FA level on the age of patients in group 1 is probably due to the ongoing formation of the myelin sheaths of the spinal cord tracts.

Thus, changes in the spinal cord tracts detected by MRI tractography are obviously related to clinical manifestations of TCS. Coarse neurological deficit during tract interruption, based on MRI tractography data, suggests irreversible structural damage of the spinal cord, including structures of the propriospinal system. In addition, the clinical signs of TCS may be associated with other forms of myelodysplasia (syringomyelia, diastematomyelia and others), change in presence of comorbidities (hydrocephalus, Chiari malformation and others) and due to any “external” influences (trauma, ischemia, processes of scar and adhesion formation) [4] and MRI tractography data, in turn, may vary depending on the age of a patient as well as artifacts from spinal cord pulsation and liquor flow in the terminal cistern may render MRI data difficult to interpret [18].

**Conclusions**

One may suggest from the data of this study that preservation of the spinal cord tracts, based on MRI...
tractography data, and stretch release lead to high probability of recovery from neurological deficit and, therefore, favorable prognosis of treatment. It is obvious that the phenomena revealed during MTRI tractography of the spinal cord are still poorly understood and require further study, including in patients with TCS. Hence, search for criteria of differential diagnosis of functional disorders and structural injury of tracts and segmental apparatus of the caudal spinal cord is still relevant.

**Authors declare no conflict of interest.**

**REFERENCES**


Surgical treatment of spinal cord malformations is still a topical medical concern despite implementation of modern diagnostics and treatments methods. Moreover, development of complex forms of pathology that require surgical myelomeningocele repair challenge the neurosurgeons with tasks requiring a thorough analysis of the treatment outcomes and their evaluation is based on the current methods of functional diagnostics and introscopy.

In this paper, the authors have described outcomes of surgical treatment of 21 patients who presented with tethered spinal cord at the age of 1 to 14 years.

Based on the analysis of clinical manifestations, evoked potentials, and data of tractography the authors assume that patients with filum terminale abnormalities and caudal lipomas show regression of clinical symptoms and identified improved electrophysiological manifestations of motor deficit by correlation analysis.

In patients with secondary spinal cord tethering caused by scar formation after myelomeningocele repair motor deficit remained unchanged and surgery did not result in any significant regression of clinical symptoms.

The authors conclude that coarse neurological deficit and interruption of spinal cord tracts suggest structural injury to the spinal cord and, therefore, recovery of motor and sensory functions is problematic. Further study of the phenomena detected on MRI tractography in patients with TSC probably will allow approaching prognosis of disturbed function recovery in injured tracts and segmental apparatus of the spinal cord.

One may hope that further study with accumulation of more data will allow the authors to acquire statistically significant results.

The disadvantages of this study may include a “complicated” title of the paper (I have already mentioned about this during the discussion with the first author (when using a complex structure “clinical introspective comparison” one should remember that high field MRI is only a part rather than a whole). Moreover, it would be clearer if the authors had used a 7 or 13T tomograph that would allow emphasizing the “originality” of this study and focusing on the term “high field”.

S.N. Larionov (Irkutsk, Russia)
Radiotherapy of Primary Intraocular Lymphoma Associated With Primary Central Nervous System Lymphoma

O.F. TROPINSKAYA, E.R. VETLOVA, N.K. SEROVA, A.V. GOLANOV, N.A. FIL’CHENKOVA

Burdenko Neurosurgical Institute, Moscow, Russia

Aim. The aim of the study was to define indications for stereotactic radiotherapy (SRT) of primary intraocular lymphoma (PIOL) and to evaluate the SRT efficacy and toxicity level.

Material and methods. Twelve immunocompetent patients with PIOL associated with primary CNS lymphoma underwent SRT of the affected eye/both eyes area. Three patients underwent repeated SRT due to PIOL recurrence.

Results. An improvement in visual acuity occurred in 6 patients. No changes in the visual function were observed in patients with high visual acuity, patients with amaurosis, and patients with concomitant eye diseases. Tumoral infiltration of the vitreous body resolved/decreased in all patients, except one case with retinal PIOL. PIOL recurrence developed in 6 patients. The disease-free period ranged from 1 to 24 months. The development/progression of cataract was found in 2 patients. Temporary radiation epidermitis occurred in 7 patients. One patient had lower eyelid ectropion.

Conclusion. SRT is indicated for PIOL recurrence after intravitreal methotrexate injections, and in the case when local chemotherapy can not be used. In the case of combined injury to the brain and eyes, it is recommended that planned whole brain irradiation to involve the eyeball area. Local SRT is recommended if lymphoma locally affects the eye (or both eyes) without involvement of the brain. PIOL radiotherapy enables achieving persistent local disease control with minimal toxicity manifestations.

Keywords: primary intraocular lymphoma, primary CNS lymphoma, radiotherapy.

Abbreviations

WBRT — whole-brain radiation therapy
PIOL — primary intraocular lymphoma
PCNSL — primary central nervous system lymphoma
PCR — polymerase chain reaction
SRD — single radiation dose
SRT — stereotactic radiotherapy
TRD — total radiation dose

Primary PIOL is a subtype of PCNSL, it comprises 2—3% of all non-Hodgkin lymphomas and occurs in 3—4% of patients with brain tumor, it is more common among people older than 60 years [1, 2]. According to different authors [2—5], PIOL occurs in 11—25% of patients with PCNSL. Morphological diagnosis of both PIOL and PCNSL is presented by B-cell variant in more than 90% of cases [6]. PIOL usually causes damage to the vitreoretinal complex and is bilateral [2—5, 7], accompanied by deterioration of visual functions, precipitates on the corneal endothelium (accumulation of B-cell lymphocytes), lymphoid infiltration of the vitreous body, and subretinal infiltrates. At the terminal stage of the disease, PIOL causes traction retinal detachment resulting in the functional death of an eye and amaurosis.

The main methods of instrumental diagnostics of PIOL are anterior segment biomicroscopy, ultrasound examination of the eyeball in vitreous mode, fundus ophthalmoscopy in the condition of medication mydriasis.

In 2012, we were the first to publish our own preliminary results of the treatment of 7 patients with PIOL who underwent trans-scleral intravitreal injections of methotrexate through the flat portion of the ciliary body [8]. Four of these patients had PIOL recurrence. A decision was made to perform radiotherapy as part of the combined treatment of PIOL or independent treatment in case of impossibility to perform chemotherapy in the first stage of treatment.

An experience of PIOL radiotherapy is presented in the foreign literature [2, 5, 7, 9, 10]. R. Mikami et al. [10] reported 22 immunocompetent patients with PIOL who underwent SRT with TRD of 30.0 to 40.0 Gy. The authors concluded that 81% of patients had an increase of visual function or their stabilization after SRT, cataract developed in 5 patients and, in general, a local control of the tumor was achieved as a result of SRT. There are no data on PIOL radiotherapy presented in the Russian literature, which determines the relevance of this study [3, 11, 12].

The aim of this research is to define indications for SRT of PIOL and evaluate SRT efficacy and toxicity level.

Material and methods

The study included 12 immunocompetent patients (7 females aged 41 to 74 years and 5 males aged 47 to 57 years, the mean age of all patients was 58 years) with
PIOL associated with PCNSL who received treatment at Burdenko Neurosurgical Institute in the period of 2011 to 2015 (Table 1).

In 10 patients, PIOL was diagnosed by clinical and instrumental methods. Two patients had previously undergone partial vitrectomy with aspiration biopsy of the vitreous body*. Further, PCR analysis detected B-cell clonality of immunoglobulin heavy chain gene rearrangements**. PIOL appeared 1—2 years prior to clinical manifestations of PCNSL in half of the cases (6 patients) and developed by the time of brain lymphoma detection. In 3 patients, PIOL was detected simultaneously with PCNSL, and 3 patients developed PCNSL 6, 30 and 31 months after PCNSL treatment onset. As the first-line treatment of PCNSL, 11 patients underwent intra-arterial chemotherapy with methotrexate with temporary opening of the blood-brain barrier. Of these, 2 patients received a course of trans-scleral intravitreal injections of methotrexate into the eyeball affected by lymphoma*. In case of occurrence of PCNSL progression after intra-arterial chemotherapy (8 patients) or refused chemotherapy (1), WBRT was conducted. All patients with PIOL underwent radiotherapy of the area of the affected eye (9 cases: both eyes, 3 cases: one eye)***. Three patients underwent repeated SRT of the same eye against the background of developed PIOL recurrence but not earlier than 1 year after the first course of radiotherapy. In simultaneous detection of brain lymphoma and PIOL lesion foci, both brain and the affected eyeball were included in the radiation zone (6 patients). The target was the whole brain and eye (both eyes). Irradiation was conducted 5 times a week in 20 fractions with SRD=1.8 Gy to TRD avg.=36.0 Gy. Critical structures of the brain and eye were within tolerance. Single local irradiation of the eyeball was performed in 8 patients in PCNSL recurrence and the presence of active PIOL manifestations. SRT was conducted in 20 fractions with SRD=1.8—2.0 Gy to TRD avg.=36.0—40.0 Gy. Critical structures (optic nerve, retina) remained within tolerance level. Radiotherapy was performed on Primus and Novalis linear accelerators with micromultileaf collimator and radiation energy of 6 MeV. Mask patient immobilization had been previously performed followed by topometric computed tomography. Pre-radiation preparation was performed on Amphora and iPlan planning systems. Target volume was included in 90% isodose curve in planning of SRT on the eyeball area (GTV=CTV).

Results

Improvement in visual acuity and disappearance of precipitates on the corneal endothelium were noted in 6 patients (Table 2) after PIOL radiotherapy. Visual

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*On the basis of Moscow Ophthalmology clinical hospital with participation of ophthalmic oncologist Professor E.E. Grishina.

**At the laboratory of molecular hematology of Hematology Research Center RAMS.

***At the department of radiology and radiosurgery at Burdenko Neurosurgical Institute.
functions remained without dynamics in case when the patient had high visual acuity (visus=1.0) or when the eye affected by lymphoma was blind prior to SRT (2 patients). In addition, no dynamics of visual function were observed in 4 patients who had concomitant ocular diseases (cataract, macular degeneration, retinal degeneration).

Control ultrasound examination after SRT showed reduction/disappearance of infiltration of the vitreous body by lymphoma cells in 11 patients. The exception was 1 case with prevailing subretinal lymphoma lesions. Pain released in 1 patient with end-stage PIOL after SRT.

PIOL recurrence after SRT developed in half of the cases (6 patients); disease-free period ranged from 1 to 24 months. Development/progression of cataract requiring surgery was noted in 2 patients during eyeball irradiation. Modern capabilities of ophthalmic surgery can provide the solution for this problem. Temporary radiation epidermitis was observed in 7 patients. Three patients developed ocular hypertension arrested by antihypertensive drops. A 74-year-old patient had lower eyelid ectropion after SRT of intraocular lymphoma.

**Clinical case**

Patient L., aged 41, was first admitted to Burdenko Neurosurgical Institute in 2010 with the diagnosis of tumor of the left posterior parietal region, which was manifested by epileptic seizures and motor aphasia. She underwent surgery for removal of intracerebral tumor with intraoperative mapping of speech and motor centers. Morphological diagnosis: B-cell lymphoma with positive expression of specific markers (OLA, CD 10, CD 20).

A total of 9 sessions of intra-arterial chemotherapy with methotrexate with preliminary opening of the blood-brain barrier were conducted. A complete response to the treatment was achieved. Disease-free period was 19 months.

Alongside with clinical manifestations of PCNSL, initial stage of PIOL of both eyes was detected during examination by an ophthalmologist. PCR was conducted after partial vitrectomy with aspiration biopsy of the vitreous body, which revealed B-cell clonality of immunoglobulin heavy chain gene rearrangements. A total of 25 of trans-scleral methotrexate injections into the vitreous body of the right eye were performed.

Positive dynamics was noted at the end of treatment in the form of tumor stabilization. However, complicated cataract developed. Surgery on cataract extraction with intraocular lens implantation was carried out. Three months after intravitreal injections, PIOL recurrence of the right eye appeared (Fig. 1a), SRT was performed.

We used a Novalis linear accelerator with micro-multileaf collimator. Irradiation was carried out using three dynamic arcs with one isocenter, with the protection

**Table 2. Results of PIOL radiotherapy, complications and post-radiation reactions**

<table>
<thead>
<tr>
<th>Patient №</th>
<th>Dynamic of visual functions after radiotherapy</th>
<th>Dynamic of ultrasound data after radiotherapy</th>
<th>Terms of PIOL recurrence development after radiotherapy, months</th>
<th>Complications and post-radiation reactions</th>
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<td>1</td>
<td>OD — no dynamics (visus*=0) OS — improvement (0.2 to 0.5)</td>
<td>Improvement</td>
<td>OS — 7</td>
<td>Radiation epidermitis, cataract</td>
</tr>
<tr>
<td>2</td>
<td>OD — improvement (0.8 to 1.0) OS — improvement (0.7 to 0.9) OD (relapse) — improvement (0.7 to 1.0)</td>
<td>Improvement</td>
<td>OD — 24</td>
<td>Radiation epidermitis</td>
</tr>
<tr>
<td>3</td>
<td>OD — no dynamics (visus=1.0) OS — no dynamics (visus=0)</td>
<td>No dynamics (retinal PIOL)</td>
<td>OD — 12</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>OS — improvement (0.5 to 0.8)</td>
<td>Improvement</td>
<td>OS — 12</td>
<td>Radiation epidermitis</td>
</tr>
<tr>
<td>5</td>
<td>OS — no dynamics (cataract)</td>
<td>Improvement</td>
<td>—</td>
<td>Radiation epidermitis, cataract, ocular hypertension</td>
</tr>
<tr>
<td>6</td>
<td>OD — improvement (0.4 to 0.7) OS — no dynamics (visus=1.0)</td>
<td>Improvement</td>
<td>—</td>
<td>Radiation epidermitis</td>
</tr>
<tr>
<td>7</td>
<td>OD — no dynamics (cataract) OS — no dynamics (visus=1.0) OD (relapse) — improvement (0.6 to 0.8)</td>
<td>Improvement</td>
<td>OD — 18 OS — 21</td>
<td>Ocular hypertension</td>
</tr>
<tr>
<td>8</td>
<td>The research is unreliable</td>
<td>Improvement</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>OD — improvement (0.5 to 0.8) OS — improvement (0.5 to 0.7) OD (relapse) — improvement (0.1 to 0.3)</td>
<td>Improvement</td>
<td>OU — 1 month</td>
<td>Radiation epidermitis</td>
</tr>
<tr>
<td>10</td>
<td>OS — no dynamics (visus=0)</td>
<td>Improvement</td>
<td>No data</td>
<td>Ocular hypertension, lower eyelid ectropion</td>
</tr>
<tr>
<td>11</td>
<td>OU — no dynamics (retinal degeneration)</td>
<td>Improvement</td>
<td>No data</td>
<td>Radiation epidermitis</td>
</tr>
<tr>
<td>12</td>
<td>OU — no dynamics (macular degeneration)</td>
<td>Improvement</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Footnote. *visus — visual acuity

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PROBLEMS OF NEUROSURGERY NAMED AFTER N. N. BURDENKO 3, 2016
of critical structures (optic nerve and retina). Target volume \( \text{GTV=CTV=7.516 cm}^3 \) was included in the 80% isodose curve (Fig. 2).

A total of 20 fractions with \( \text{SRD=1.8 Gy to TRD avg.=36.0 Gy} \) were conducted in the course of the treatment. Irradiation was carried out 5 days a week. Ocular hypertension appeared during radiation therapy, which was arrested by Sol. Arutimoli 0.5% installations.

As a result of SRT, complete regression of PIOL was achieved (see fig. 1, b); disease-free period was 18 months. Then, precipitates on the corneal endothelium and increased infiltration of the vitreous body by

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**Fig. 1.** Ultrasound examination of the right eyeball in vitreous mode.  
0 — recurrent intraocular lymphoma (indicated by arrow) prior to SRT;  
b — regressed lymphoma 1 month after SRT.

**Fig. 2.** Isodose distribution in SRT of intraocular lymphoma on a Novalis linear accelerator.

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**Fig. 3.** MRI of the brain in the axial projection: on the left — in T1 mode, on the right — in FLAIR T2 mode (contrast accumulation focus in the right parietal region).
lymphoma cells appeared, which were considered as local recurrence. At the same time, control MRI of the brain revealed the focus of contrast accumulation in the right parietal region: relapsed lymphoma of hemispheric localization (Fig. 3).

A course of SRT was performed on a Primus linear accelerator**: “whole brain and the right eye” target (PTV=1328.8 ccm) was subjected to 20 fractions with SRD=1.8 Gy to TRD avg.=36.0 Gy in the classical fractionation mode (Fig. 4).

Control brain MRI after irradiation revealed no contrast accumulation in the right parietal region or appearance of new lymphoma foci (Fig. 5).

Positive dynamics were also noted on the part of the eye: precipitates on the corneal endothelium resolved, infiltration of the vitreous body by lymphoma cells

\[\text{Fig. 4. WBRT plan with simultaneous radiation of the affected eyeball on a Primus linear accelerator.}\]

Isodose distribution, field orientation.
became less intense. Disease-free period was 9 months to date.

After completion of local chemotherapy of PIOL of the right eye, a course of chemotherapy of PIOL of the left eye was performed (20 intravitreal injections of methotrexate),* which resulted in remission. Disease-free period was traced for 5 months. In connection with recurrence of PIOL of the left eye, SRT on a Novalis linear accelerator was performed;*** a total of 20 fractions with of SRD=2.0 Gy to TRD avg.=40.0 Gy were administered. Complete regression of PIOL was achieved at the end of SRT. Recurrence appeared after 21 months. There is an ongoing issue on whether to perform repeated SRT.

**Discussion**

The development of modern methods of brain malignancy treatment changed the quality and duration of patients’ life. PCNSL and PIOL are a multidisciplinary problem and require participation of a pathologist, radiologist, neurosurgeon, chemotherapist, radiologist, ophthalmologist, and hematologist. B-cell lymphoma of CNS is known to have high sensitivity to ionizing radiation, which allows using radiotherapy as an effective method of treatment of this malignant tumor. Combined lesion of both B-cell lymphoma of the brain and eyeballs is an evidence of its tropism to these target organs [3, 8]. Clinical manifestation of PIOL can outpace the development of PCNSL. In this case, a so-called masquerade syndrome occurs when such diseases as uveitis, vitritis, hemophthalmia, diffuse retinal vasculitis, and chorioretinitis are misdiagnosed, and anti-inflammatory or glucocorticoid therapy carried out on this basis turns out to be ineffective [3, 4, 7, 12—15]. B-cell lymphoma can be detected both in the brain and eyeball. Less frequently, delayed development of PIOL takes place after successful treatment of PCNSL or recurs after local chemotherapy, radiotherapy in the absence of the signs of brain damage. The question arises: how to treat these patients in each particular case?

We have developed and adopted the following algorithm based on our own experience of treating PIOL. If clinical manifestations of PIOL were observed at the stage of WBRT, the affected eyeball was included in the irradiation area during radiotherapy planning. In case of primary lesion of the eyeball in the absence of signs of disease in the brain or in the case of PIOL recurrence after methotrexate administration in the eye cavity, SRT of intraocular lymphoma was carried out locally on the eye area. Radiation doses, as in the case of local SRT and WBRT including the area of eyeballs, were the same. Taking into account the potential total toxicity of radiotherapy, the same dose was used for different stages of PIOL and its recurrence.

Implementation of SRT in a rare form of PIOL primarily affecting the retina allowed to delay the onset of amaurosis of the only sighted eye [15]. Recurrence with traction retinal detachment developed 12 months after SRT, and this eye was blind.

Of particular interest, in our opinion, is a clinical case of patient L. presented above, who underwent repeated SRT with an interval of 2.5 years, and remission for 9 months was achieved by the time of this article’s writing.

SRT duration averages 1 month, course treatment with methotrexate administration in the eye cavity is conducted for 9 months. After intravitreal injection of methotrexate, 2 out of 7 patients developed complicated cataract, which is comparable with the number of 2 patients with post-radiation cataract. There were no cases of post-radiation retinopathy, which are mentioned in the literature, in our series of patients [9]. Comparing the effects of SRT and PIOL chemotherapy, it can be noted that eye radiation as a non-invasive treatment method was tolerated more easily by patients.

**Conclusion**

The use of radiation therapy is indicated in PIOL recurrence after intravitreal injections of methotrexate, as well as in the case of impossible implementation of local chemotherapy program. In case of combined damage to the brain and eye and decision on whether to perform WBRT, it is appropriate to include eyeballs in the area of radiation when planning radiation therapy. In isolated lymphoma lesion of an eye (or both eyes) and no signs of disease manifestations in the brain, local SRT is appropriate. PIOL radiotherapy allows achieving persistent local control over disease with minimal toxicity.

Authors declare no conflict of interest.
The existence and successful work of modern radiology department at Burdenko Neurosurgical Institute has dramatically changed the approaches to the treatment of patients with oncological diseases not only of neurosurgery profile but also and other related specialties. In particular, it concerns such interdisciplinary problem as primary intraocular lymphoma. The authors presented the first Russian experience of using radiotherapy in this pathology with good results: a persistent control over disease and minimal manifestations of radiotoxicity. An already approved algorithm of interventions has been proposed based on the presence of lesion in the brain, as well as the use of chemotherapy in the course of treatment. In my opinion, the presented data is extremely necessary and demanded in the practice of physicians of various specialties: neurosurgeons, ophthalmologists, radiologists, chemotherapeutists, and hematologists, who are involved in the treatment of primary intraocular lymphoma.

V. A. Lazarev (Moscow, Russia)
An increased blood level of the thyroid-stimulating hormone (TSH) is usually associated with primary hypothyroidism (PHT) but can also be observed in such rare cases as TSH-secreting pituitary tumor. Four clinical cases of elevated TSH blood levels are reported: 1) TSH-secreting pituitary adenoma with hyperthyroidism; 2) TSH-secreting adenoma with hypothyroidism; 3) hormone-inactive pituitary adenoma associated with primary hypothyroidism; and 4) reversible thyrotropic hyperplasia. These clinical situations substantiate the importance of considering different diagnoses in a patient with a pituitary gland tumor associated with the increased TSH blood level.

**Keywords:** TSH-secreting pituitary adenoma, thyrotropin-secreting adenoma, central hyperthyroidism, thyrotropic hyperplasia, primary hypothyroidism.

**Abbreviations**

- **PA** — pituitary adenoma
- **TPOAb** — thyroid peroxidase antibodies
- **HIPA** — hormone-inactive pituitary adenoma
- **IHC study** — immunohistochemical study
- **IGF-1** — insulin-like growth factor 1
- **OGTT** — oral glucose tolerance test
- **PHT** — primary hypothyroidism
- **PRL** — prolactin
- **STH** — somatotropic hormone
- **FT3** — free T3
- **FT4** — free T4
- **TRH** — thyrotropin-releasing hormone
- **TSH** — thyroid-stimulating hormone
- **TSH-oma** — TSH-secreting pituitary adenoma
- **ETSA** — endonasal transphenoidal adenomectomy
- **LT4** — levothyroxine

The increased blood level of thyroid-stimulating hormone (TSH) is usually associated with primary hypothyroidism (PHT) but can also be observed in such rare cases as TSH-secreting pituitary tumor (TSH-oma); patients with resistance to thyroid hormones that is characterized by reduced sensitivity of the target tissues to thyroid hormones; as well as a number of other reasons (adrenal insufficiency, severe somatic symptom and mental disorders, administration of some medications, etc.).

Prevalence of pituitary adenomas (PA) reported by different authors [1, 2] is 78—115.5 per 100,000 population. Hormone-inactive tumors are revealed most commonly: they prevail among middle-aged and elderly patients. Cases of combined pathologies, such as pituitary adenoma and primary hypothyroidism, are also common in neuro-endocrinological practice.

Hypothyroidism is a common condition. Its prevalence among adults varies from 0.2 to 10% and is age- and sex-dependent. Women have this condition 8—10 times more often than men do; susceptibility to hypothyroidism increases progressively with age in patients of both sexes. In some countries, it is as high as 9—16% among adults older than 60 years. The most typical cause of hypothyroidism is chronic autoimmune thyroiditis, whose markers include the increased titer of antithyroid antibodies and ultrasonographic signs of an autoimmune pathology. Patients with PHT have a reduced level of thyroid hormones and an increased blood TSH level [3—6].

Patients with longstanding uncompensated PHT may develop hyperplasia and hypertrophy of pituitary thyrotropic cells caused by disruption of regulatory connections in the hypothalamus—pituitary gland—thyroid gland system. In patients with PHT, the pituitary gland enhances secretion of TSH by pituitary cells in order to stimulate the function of the thyroid gland and compensate for hypothyroidism. Hyperplasia is usually reversible by administering an adequate dose of LT4 [7, 8]. However, cases of formation of pituitary adenomas associated with hyperplasia in patients with untreated hypothyroidism have also been reported [9]. No term has been coined to refer to these tumors; however, judging from the possible nature of their development, they can be conditionally called secondary TSH-omas [10—13].

Thyrotropin-secreting pituitary tumor (TSH-oma) is a rare tumor whose prevalence among all pituitary adenomas is less than 0.5—3.0%. The criterion of TSH-oma is the increased blood level of circulating FT4 and FT3, while blood level of TSH is either increased or...
normal [14, 15]. Secretion of TSH by a primary TSH-oma stimulates enhanced production of thyroid hormones. The clinical presentation of a small-sized TSH-oma may only include hyperthyroidism, which is analogous to that of toxic diffuse goiter; hence, early diagnosis of pituitary tumor is complicated. Clinical presentation of tumors with extrasellar extension will additionally include symptoms of compression of the chiasmatic-sellar structures, such as visual and oculomotor disturbances, cephalgic syndrome, etc. [16]. Most of the tumors that have been described in literature are macroadenomas having an aggressively infiltrative growth pattern that are difficult to remove radically.

We report four clinical cases of patients with increased TSH blood level. Despite the similarity of their clinical, laboratory test, and MR signs, the strategies of managing these patients differed significantly. The main data for the clinical cases no. 1—4 are summarized in Table.

The following reference values were used when assessing the thyroid status: TSH, 0.4—4.0 mU/l; FT4, 11.5—22.7 pmol/l; and FT3, 3.5—6.5 pmol/l.

Clinical case 1. TSH-secreting pituitary adenoma causing hyperthyroidism

A 38-year-old male patient was admitted to the hospital with complaints of headache, palpitations, irritability, erectile dysfunction, and decreased libido.

Examination showed the following levels: TSH, 4.28 mU/l; FT4, 23.6 pmol/l; FT3, 12.6 pmol/l; PRL, 420 mU/l (Table). IGF-1, 386 (109—284) ng/ml. After the oral glucose tolerance test, the STH level was suppressed to less than 1.0 ng/ml. MRI examination revealed a small-sized pituitary adenoma of endosuprasellar localization (Fig. 1a, b). Data of ultrasound scanning of the thyroid gland: total volume, 14 ml; diffuse alterations.

Endoscopic endonasal transsphenoidal adenomectomy (ETSA) was carried out. Immunohistochemical study of the resected tumor confirmed the presence
of TSH (Fig. 1c), STH, and PRL-positive cells in it. Decreased TSH, FT3 and cortisol levels, normalization of the FT4 level, and symptoms of adrenal insufficiency were observed postoperatively. Hydrocortisone therapy was prescribed. Examination 1.5 months after surgery showed the following levels: TSH, 0.01 mU/l; FT4, 7.0 pmol/l; FT3, 2.29 pmol/l; IGF-1, 82.4 ng/ml (109—284), testosterone, 2.7 nmol/l; PRL, 6 µIU/ml. The patient was diagnosed with panhypopituitarism (secondary hypothyroidism, hypocorticism, hypogonadism, STH deficiency, and hypoprolactinemia). Therapy was supplemented with medications containing LT4 and testosterone. No data attesting to tumor recurrence were obtained 6 months after the surgery. The patient receives hormone replacement therapy (Table).

Clinical case 2. TSH-secreting pituitary adenoma in a female patient with PHT

A 39-year-old female patient. At the age of 38, the patient consulted an endocrinologist with complaints of a 4-year history of severe headaches, amenorrhea, swelling, and hot flushes. Examination showed the following levels: TSH>75 mU/l; FT4, 7.7 pmol/l; PRL, 2904 mU/l; TgAb, 117 U/ml (Table). Data of ultrasound scanning of the thyroid gland: abnormal echo structure; total volume, 12 ml. MRI examination showed an endosuprasellar pituitary adenoma with a cystic component (Fig. 2a, b). Therapy with 100 µg/day LT4 and cabergoline was prescribed at a community-based hospital; cabergoline was later cancelled at the Burdenko Neurosurgical Institute. The dose of LT4 was gradually increased to 175 µg/day. After 5 months, the patient consulted physicians at the Burdenko Neurosurgical Institute, having complaints of severe headache. Examination showed the following levels: TSH, 13.5 µIU/ml; FT4, 22.0 pmol/l; FT3, 7.31 pmol/l; IGF-1, 157 ng/ml. Follow-up MRI scanning showed no significant changes in tumor size. A decision was made to perform ETSA because of the pronounced cephalic syndrome and no decrease in tumor size. An ICH study
of the resected tumor confirmed that it contained TSH-positive cells (Fig. 2c). Furthermore, expression of STH and PRL in tumor was detected. Follow-up examination after 6 months showed that the levels of TSH and free thyroid hormone fractions normalized after LT4 therapy (75 µg): TSH, 2.18 IU/l; FT4, 13.4 pmol/l; FT3, 3.72 pmol/l (Table). MRI scan after gross-total resection of the tumor.

Clinical case 3. Hormone-inactive pituitary adenoma associated with primary hypothyroidism

A 54-year-old female patient was admitted with complaints of severe visual impairment and headache. Her past medical history was remarkable for hypothyroidism diagnosed 4 years earlier; she occasionally received the prescribed LT4 medication. Examination showed the following levels: TSH, 218 µIU/ml; FT4, 4.2 pmol/l; PRL, 521 mU/l; TPOAb>300 U/ml (Table). MRI scanning showed an endosuprasellar pituitary adenoma (Fig. 3a, b) and chiasmal syndrome accompanied by the development of amaurosis fugax in the left eye. Data of ultrasound scanning of the thyroid gland: total volume, 48 cm³, multiple nodes, the maximal node size 13 mm. The patient received inpatient treatment with LT4; however, taking into account visual impairment, a decision was made to perform ETSA. IHC examination of the resected tumor revealed no expression of pituitary hormones, but the hyperplased adenohypophyseal tissue with pronounced expression of TSH was found (Fig. 3c, d). The TSH level was normalized after the surgery to 1.3 mU/l; FT4 level decreased to 8.6 pmol/l (Table).

Clinical case 4. Pituitary hyperplasia associated with primary hypothyroidism

A 41-year-old female patient consulted physicians at the Burdenko Neurosurgical Institute with complaints of fatigue, weight gain, swelling, drowsiness, and headache. Examination showed TSH>75 mU/l; FT4, 4.2 pmol/l; PRL, 2065 mU/l; TPOAb, 296.0 U/ml (Table). MRI showed an endosuprasellar neoplasm, larger than the normal size of the pituitary gland approximately twofold (Fig. 4a, b). Data of ultrasound scanning of the thyroid gland: total volume, 12.4 ml; a nodule in the right lobe 16×11×11 mm in size (the patient has chronic autoimmune thyroiditis). The patient received LT4 therapy (100 µg/day). After 2 months of therapy: TSH, 0.13 mU/l; FT4, 17.2 pmol/l; PRL, 443 mU/l (Table). MRI examination 2 months after LT4 therapy had been started showed significant regression of the pituitary tumor (Fig. 4c, d).
Discussion

The pituitary origin theory is currently predominating: it suggests that the overwhelming majority of pituitary adenomas result from genetic damage in a single cell. The cell subsequently undergoes malignant transformation, clonal expansion, and adenoma formation. Most TSH-omas are plurihormonal tumors that originate from a pituitary stem cell and have a potential for differentiation into different directions. 30–40% of TSH-omas are characterized by hypersecretion of other pituitary hormones: most commonly, STH and PRL and, less commonly, gonadotropins (LH/FSH). Even in case of hypersecretion of TSH only, genetic analysis reveals expression of the STH and PRL genes [17, 18]. Hypersecretion of TSH by the tumor tissue results in hyperstimulation of the thyroid gland, therefore, hypersecretion of FT4 and FT3 [11]. It is the so-called central hyperthyroidism. Its clinical manifestations include signs of hyperthyroidism and, for large-sized tumors, signs of the tumor mass-effect (vision and neurological impairment).

Disruption of hypothalamic regulation is also an important component of oncosis in the anterior pituitary. Hence, chronic hypofunction of the peripheral endocrine glands induces constant hypothalamic stimulation followed by hyperplasia and formation of a pituitary tumor [9, 13, 19—22]. It is well-known that patients with clinical PHT have an increased blood level of TSH and reduced blood level of FT4. The patients who have not been receiving long-standing thyroid hormone therapy may develop hyperplasia of thyrotropic cells because these hormones do not have an inhibitory effect on the pituitary gland. In its turn, this increases secretion of TRH (thyreotropin-releasing hormone) that stimulates the pituitary gland, which manifests as the development

Fig. 4. Clinical case 4.

a, b — preoperative MRI scans; c, d — MRI scans after LT4 therapy for 2 months.
of hyperplasia of thyrotropic cells. Cases of compression of optic nerves by the hyperplased pituitary gland and emergence of neuro-ophthalmic symptoms have been reported (quoted after [7]).

Enhanced secretion of TRH by the pituitary gland may result not only in hyperplasia of thyrotropic cells and increased secretion of TSH, but also in hyperplasia of lactotropic cells and increase in synthesis and secretion of PRL, which is accompanied by an elevated blood level of PRL and clinical manifestations of hyperprolactinemia [23]. Hyperplasia of thyrotropic cells are a result of PHT is most commonly observed among women and is typically reversible by using adequate doses of thyroid hormones, which manifests by normalization of TSH, FT4, FT3, and PRL levels.

However, prolonged stimulation with TRH may result in the formation of the so-called secondary TSH-oma [10]. N. Ryan [9] studied post mortem samples from the pituitary gland tissue of 64 patients with chronic hypothyroidism and revealed hyperplasia of thyrotropic cells in most cases. Diffuse hyperplasia of thyrotropic cells was detected in 69% of the samples, while nodular hyperplasia was observed in 25% of the samples. In 12% of the samples, alterations were considered to be the intermediate stage between nodular hyperplasia and microadenoma. Five cases of TSH-positive pituitary microadenomas were identified. Lactotropic hyperplasia was observed in 20% of the samples.

Differential diagnosis (including MR signs) between adenohypophysial hyperplasia and true pituitary adenoma in patients with primary hypothyroidism is often complicated. As a result, it is challenging to select a proper therapy method as they differ fundamentally for these pathologies. Thus, LT4 therapy is effective in thyrotropic hyperplasia associated with primary hypothyroidism: it normalizes the level of thyroid hormones, reduces the TSH level and results in regression of thyrotropic hyperplasia, which manifests itself as a reduction in volume in the chiasmatic-sellar region. Treatment duration usually varies from 1 to 4 months, although in some cases regression of the tumor in the chiasmatic-sellar region can be observed during the first week of LT4 therapy [24, 25]. After patients with pre-existing hyperprolactinemia achieve euthyroidism, their PRL level normalizes and menstrual cycle recovers. Therefore, prescribing dopamine agonists before compensation of hypothyroidism is unreasonable. However, it is more likely that a patient has prolactinoma

Fig. 5. Possible reasons for the elevated TSH level in patients with a bulky pituitary tumor and the treatment algorithm.
if LT4 therapy normalizes the TSH and FT4 levels, while the level of PRL remains high, clinical symptoms of hyperprolactinemia are present, and adenoma size does not decrease [21]. If a patient with PHT exhibits only a partial decrease in TSH level and no MR signs of tumor regression are observed after 3—4 months of therapy with an adequate dose of LT4, then one should consider the possible development of autonomous secretion of TSH by the tumor (secondary TSH-oma); however, LT4 therapy is not effective in these cases. The method of choice for treating these patients is surgical adenomectomy followed by permanent LT4 replacement therapy [20, 22].

We have reported four different clinical cases accompanied by the increased blood level of TSH: TSH-oma causing hyperthyroidism, TSH-oma associated with PHT (secondary TSH-oma), combination of hormone-inactive adenoma and primary hypothyroidism, and reversible pituitary hyperplasia associated with primary hypothyroidism.

In the patient with TSH-oma with clinical manifestations of hyperthyroidism, an IHC test confirmed that TSH, STH, and PRL were expressed in the tumor. For pituitary adenomas accompanied by increased TSH and FT4 levels, the diagnosis of TSH-oma is usually beyond doubt. It is reasonable to analyze the PRL, STH, and IGF-1 levels and, in some cases, to measure the STH level during the oral glucose tolerance test in order to rule out mixed hormonal secretion. Successful cases of treating of TSH-oma using somatostatin analogues and dopamine agonists have been reported in literature [26, 27]; however, surgical management remains the most effective treatment (Fig. 5).

In the female patient with primary hypothyroidism (clinical case 4), LT4 therapy resulted in euthyroidism and regression of the pituitary tumor and was recognized as hyperplasia of thyrotropic cells. No significant reduction of tumor size was observed in clinical case 2, despite the decrease in the TSH level. The possibility of development of a secondary TSH-oma associated with untreated PHT should not be left out of consideration. It is quite possible that the tumor developed in the presence of hyperplasia of pituitary thyrotropic cells as it has been reported in some earlier studies [14, 20]. The patient received surgical treatment (IHC test confirmed expression of TSH, STH, and PRL in the tumor tissue).

Since primary hypothyroidism is highly prevalent among the population, this pathology is detected quite frequently among patients with pituitary adenomas, mostly the hormone-inactive one, which are predominantly observed among older patients. We have described a female patient (clinical case 3) with long-lasting untreated hypothyroidism who had been operated on for severe neuro-ophthalmic symptoms. Histological study of the resected tumor revealed a combination of TSH-negative pituitary adenoma and thyrotropic hyperplasia of the pituitary gland.

Nevertheless, all patients with hypothyroidism require drug therapy to achieve euthyroidism by the follow-up dynamic MRI of the brain. Surgery decision can be made only provided that there is neither regression nor clinical manifestations of the tumor mass effect, while the euthyroidism is achieved.

The reported clinical cases substantiate the importance of considering different diagnoses in a patient with pituitary tumor accompanied by increased blood

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TSH-secreting pituitary tumors (TSH-omas) are tumors consisting of thyrotropic cells of the pituitary gland. Hypersecretion of TSH by these tumors results in hyperstimulation of the thyroid gland and clinical manifestations of hyperthyroidism. Today, endoscopic endonasal transsphenoidal adenomectomy is the main effective method for treating TSH-omas. However, cases of pituitary hyperplasia that develops in patients with longstanding uncompensated hypothyroidism and is accompanied by increased blood level of TSH are quite frequent in clinical practice. This condition is usually treated by thyroid hormone replacement therapy.

It is not always possible to differentiate between hyperplasia and pituitary adenoma using MRI data. The treatment principles are fundamentally different for these diseases. A pituitary neoplasm detected in an MRI scan accompanied by the elevated blood level of TSH can result in misdiagnosing a TSH-secreting pituitary tumor and, therefore, improper selection of a surgical treatment strategy.

Different cases of pituitary tumors accompanied by increased TSH level, their differential diagnosis and treatment methods are described in this paper. The publication will be of interest for medical practitioners in different disciplines: neurosurgeons, radiologists, endocrinologists, and morphologists.

F.M. Abdulkhabirova (Moscow, Russia)
Neurosurgery in a Patient on Dual Antiplatelet Therapy. Case Report and the Review of the Literature

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Burdenko Neurosurgical Institute, Moscow, Russia

Introduction. A neurosurgical intervention in a patient on dual antiplatelet therapy is a serious challenge for both the neurosurgeon and anesthesiologist.

Material and methods. The article describes a clinical case of a successful urgent neurosurgical intervention (ventriculoperitoneal shunt for obstructive hydrocephalus caused by a large meningioma of the posterior surface of the petrous pyramid) in a patient on dual antiplatelet therapy (DAT) due to a recently placed coronary stent.

Conclusion. Given a high risk of coronary stent thrombosis, the surgery was performed in the presence of ongoing DAT. There were no intracranial hemorrhagic complications, but subcutaneous hemorrhagic complications developed. The article discusses the features of managing similar patients whose number is growing.

Keywords: neurosurgical intervention, skull base tumors, coronary stent, dual antiplatelet therapy.

An intensively developing interventional cardiology with implementation of the methods of angioplasty and stenting of the coronary arteries in the last 10—15 years is truly a breakthrough in the treatment and prevention of coronary heart disease (CHD) [1—3]. However, dual antiplatelet therapy (DAT) in the form of acetylsalicylic acid (ASA) and clopidogrel combination, which is used for stent thrombosis prevention, especially with drug coating, is prescribed for a long period: 1 to 1.6 years; and only then there is a transition to mono antiplatelet therapy with ASA [4, 5]. Effective DAT used to the full extent creates the risk of spontaneous hemorrhagic complications, while in the case when surgery is required, the risk of hemorrhagic complications on the background of DAT is increased many times [6—8]. Neurosurgical interventions undoubtedly belong to the surgeries with high risk of perioperative hemorrhagic complications, and their performance in patients receiving DAT can be a serious problem. Here we present a case from our clinical practice when an urgent neurosurgical intervention was required for the patient with a freshly placed coronary stent and receiving DAT.

Clinical case. Patient Sh., 67 years of age (body weight: 94 kg), pensioner, was admitted to Burdenko Neurosurgical Institute in July 2015 with a diagnosis of “giant meningioma of the tentorium of the cerebellum on the right. Obstructive hydrocephalus”. His medical history includes long-term CHD: exertional angina functional class III. The patient was also diagnosed with hypertension III degree, risk 4 and chronic heart failure I degree, functional class II. He suffered a Q-positive myocardial infarction of the left ventricle in 2009 and phlebectomy of varicose veins in the left leg in 2012. In 2014, radiation therapy for cancer of the lower lip was performed.

In the early 2014, he was hospitalized to the vascular unit at the place of residence with complaints of a decrease in exercise tolerance, shortness of breath and pain in the calves. Taking into account the clinical symptoms of the disease, the results of objective examination, echocardiography and coronary angiography data: hemodynamically significant lesion of the circumflex artery, the absence of anterior coronary artery lesion, high risk of recurrent myocardial infarction; it was decided to perform revascularization by angioplasty and stenting. On 03/25/15, the patient underwent the surgery of transcutaneous transluminal coronary angioplasty of the circumflex artery with Track stent implantation. After surgery, the patient took the following drugs on a constant basis: 75 mg of Plavix in the evening, 100 mg of Thrombo ASA in the morning, 20 mg of Rozukardin the evening, 50 mg of Betalocin the morning, and 50 mg of Prestarium in the evening.

After surgery, the patient began to notice unsteadiness of gait, which was accompanied with impaired urination in the form of urinary incontinence and significant decrease in memory with time. On his own initiative, he underwent computed tomography of the brain, which showed a giant meningioma of the tentorium of the cerebellum with supra- and subtentorial distribution, as well as signs of obstructive hydrocephalus with periventricular edema (Fig. 1). Magnetic resonance imaging (MRI) confirmed the diagnosis (Fig. 2). The patient was admitted to the Institute of Neurosurgery for examination and possible surgical treatment.

During examination, in the absence of signs of severe intracranial hypertension, visual acuity with correction was OD=1.5, OS=0.3. Clinical status by Karnofsky scale was 50 points. The clinical picture of the disease showed Hakim-Adams triad: gait disturbance, impaired urination in the form of urinary incontinence and memory impairment. Stem and cerebellar symptoms were also present. The symptoms were caused by a giant

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meningioma of the tentorium of the cerebellum on the right and obstructive hydrocephalus.

Clinical blood analysis showed thrombocytopenia 136·10⁹/l. In addition, platelet function was assessed on PFA 200 analyzer (“Simens”, Germany). The device simulates platelet adhesion and aggregation occurring during vessel injury and registers the clotting time, which is an indicator of the platelet component of the overall blood clotting time. The value of collagen/epinephrine test (detection of ASA effect) was greater than 300 sec (normal range: up to 160 sec). The value of P2Y test (detection of the effect of drugs inhibiting P2Y12 receptors: in this particular case, Plavix) reached 143 sec (normal range: up to 106 sec). Thus, the performance of both DAT components was effective. Normal coagulation with a tendency to hypocoagulation was revealed by conventional thromboelastography on 08/22/15.

Consultation result: taking into account the serious condition of the patient, severe hydrocephalus with periventricular edema, burdened somatic status, administration of antiplatelet drugs (DAT) and impairment of the blood coagulation system caused by it and confirmed by examinations, as well as thrombocytopenia, ventriculoperitoneal shunt was prescribed as the first step for the patient with the further decision of possible radiation treatment. Taking into account the high risk of stent thrombosis (less than 6 months from the date of installation), the decision was made not to cancel antiplatelet drugs either before or after surgery.

On 07/23/15, the patient underwent ventriculoperitoneal shunting on the left side. Rapid improvement in gait, memory, and partial regression of cerebral symptoms were noted in the postoperative period. However, diffuse subcutaneous hematomas in the area of the installed shunt system and under the left eye drew attention. Examination by ophthalmologist determined a moderate swelling of the eyelids on the left, bleeding under the skin of eyelids, and subconjunctival hemorrhage (Fig. 3).

No intracranial hemorrhagic complications were found during spiral computed tomography (SCT) of the brain on the 1st and 4th days after surgery. Ventricular end of the catheter is located in the anterior horn of the left lateral ventricle, petrified part of the tumor is visualized in the posterior fossa (Fig. 4).

The patient was discharged from the hospital in a relatively good condition on the 4th day after surgery with the recommended consultation of a radiologist on the decision of radiotherapy administration.

Fig. 1. SCT of patient Sh.
A giant meningioma of the tentorium of the cerebellum on the right with the presence of petrifications is determined on the axial sections. Hydrocephalus with signs of periventricular edema also draws attention.
Discussion

Recently, patients with CHD and stenotic lesion of coronary arteries very often undergo angioplasty and stenting of stenotic arteries with good clinical effect, as evidenced by the results of a series of collaborative studies [1—3]. Even in 2007, there were more than one million (1,085,357) of endovascular coronary revascularization procedures performed in the United States [9] with the estimated tendency to their 0.5% increase per year [10]. One of the most severe complications of coronary angioplasty and stenting is stent thrombosis, the risk of which is especially high when using not simple metal stents but drug-eluting stents preventing epithelialization of the inner stent surface [1, 11]. In order to prevent this severe complication, the mortality from which can reach 20—50% [4, 5, 12—17], the use of DAT was proposed: a combination of clopidogrel (Plavix) and ASA (Thrombo ASA in our observation), which act on various structures of platelet membrane and effectively prevent adhesion of platelets in the majority of patients sensitive to them [4, 5]. However, administration of DAT must be constant and should not be interrupted for a year after stent installation, the longer the better. A serious clinical dilemma occurs when a patient receiving DAT requires surgical intervention, especially a neurosurgical one [6—8, 18, 19]. Withdrawal of DAT entails a higher risk of stent thrombosis, a complication with high risk of mortality. At the same time, neurosurgical interventions, most of which undoubtedly belong to the high risk

Fig. 2. MRI of patient Sh.
The signs of periventricular edema (evidence of obstructive nature of hydrocephalus) and peritumoral edema are visualized on the axial sections in T2 (a, b) and FLAIR (c, d) modes.
bleeding surgery, are associated with a high risk of perioperative bleeding. The obvious solution in such situations does not currently exist, but we are to try to figure it out.

The first. Effective antiplatelet therapy can be dangerous in relation to spontaneous hemorrhages in the central nervous system even in the absence of any surgical intervention. For example, the development of spontaneous spinal and intracranial hematomas and subarachnoid hemorrhages on the background of antiplatelet therapy was described [20—26]. In elderly patients with Alzheimer's disease, antiplatelet therapy with only ASA increases the frequency of spontaneous intracranial hemorrhage more than 3-fold [27].

The second. There is a problem of hemorrhagic complications, which is basically close to the first problem, in patients continuously receiving anticoagulants: warfarin, low-molecular-weight heparins or peroral inhibitors of thrombin and anti-Xa activity, which are becoming more widely used in clinical practice. These are patients with artificial heart valves, recurrent pulmonary artery thromboembolia and persistent forms of cardiac arrhythmias. The situation is largely similar in these patients in the case of upcoming surgery. Could this suggest some reasonable solution to our problem? There have been recommendations of the European Society of Anesthesiologists and domestic clinical guidelines on the managing this group of patients published in the past few years [28, 29], and these recommendations are similar in various aspects. They use a quite rational approach: stratification of patients according to the risk of bleeding during surgery. For example, in the case of low risk bleeding surgeries (minor gynecology, dental interventions, arthroscopy), it is proposed not to discontinue anticoagulation therapy and perform surgery on this background. In the case of the high risk bleeding surgery, it was proposed to use bridging therapy: transition to short-acting and thus highly controlled anticoagulants such as low-molecular-weight heparins with the effect duration of 10—12 h, and their withdrawal prior to surgery [28, 29]. Could this approach be used in the case of DAT in neurosurgical patients? Apparently, not.

Cerebrospinal fluid shunt surgery and even just ventriculostomy, which, on one hand, could be attributed to the low risk bleeding surgeries, turned out to be also accompanied, according to the literature [14, 30—35], by a quite high percentage of hemorrhagic complications, especially against the background of ongoing DAT, a
situation very similar to the one described in this particular case, while the use of bridging therapy with low-molecular-weight heparins or unfractionated heparin turned out to be ineffective in the prevention of coronary stent thrombosis.

The third. For the past years, due to the introduction of flow-diverting stents in the practice of endovascular neurosurgery, the problem of DAT application in such patients occurred in clinical practice [36—38]. It turned out that there is a group of patients who do not respond adequately to one or both antiplatelet agents: the so-called low-responders [39—42]. In these patients, according to laboratory tests, the effect is not observed when using standard doses of antiplatelet agents, i.e. DAT is simply not effective. Without analyzing the mechanisms of this reaction, it can be noted that the number of relatively low-responders to ASA does not exceed 10%, whereas this value for clopidogrel can reach 60% [43]. The awareness of the danger to such patients even led to the proposal of using triple antiplatelet therapy (e. g., ASA + clopidogrel + cilostazol) [44, 45]. The review by T. Wang et al. [43], taking into account the problems of low-responders, proposes implementation of daily platelet monitoring of antiplatelet effect similar to glucose measurement or INR (international normalized ratio). From the standpoint of a neurosurgeon, low-responders are a favorable group for neurosurgical intervention because they can be operated on without withdrawal of any of the prescribed drug. We had similar observations in our practice. However, this situation seems to be uncontrollable, since inefficient DAT and the effect of surgical stress can cause stent thrombosis with all of the ensuing consequences. Apparently, such approach cannot be considered acceptable, and a reasonable alternative for it can only be the dynamic laboratory monitoring using bedside methods, which have been developed and are used in clinical practice [38, 44, 46—48].

The fourth. Bridging therapy. Now it is clear that conventional bridging therapy with quick-acting and controlled anticoagulants in patients with coronary stents does not work for whatever reasons. However, there is the possibility of bridging therapy: short-acting antiplatelets, such as eptifibatide (Integrilin, “Omni- pharm”) administered intravenously as a continuous infusion. The efficacy of this approach has been proved, especially in emergency situations [49, 50].

The fifth and the last. The required terms of DAT administration. There are different recommendations regarding this issue. However, DAT administration within a year after stent placement with subsequent transition to ASA monotherapy is considered to be a widely accepted approach [51]. Analysis of the literature data, however, does not confirm the safety of this approach [52, 53].

**Conclusion**

Returning to our patient, we can say that there was an element of luck in this case. In case of required planned neurosurgical intervention in these patients, it is advisable to wait for the completion of dual antiplatelet therapy. However, taking into account the presence of giant meningioma of the tentorium of the cerebellum, progression of obstructive hydrocephalus and the risk of cerebellar tonsil herniation into the foramen magnum, it was decided to perform cerebrospinal fluid shunt surgery for health reasons. DAT was effective in this case, which was clearly confirmed by the patient’s appearance after surgery and laboratory test data. Moreover, there were no intracranial bleeding complications. However, one should not expect such favorable outcomes in similar situations. In this regard, we believe the following algorithm to be rational in the treatment of these patients:

1. Evaluation of the true efficacy of DAT received by a patient using available and informative laboratory tests (in particular, measurement of coagulation time on a PFA 200 analyzer with collagen/epinephrine and P2Y12 cartridges).

2. Expert assessment of the risk of potential hemorrhagic complications of neurosurgical intervention (this assessment requires specifications). In complex and undoubtedly risky cases: bridging therapy with short-acting antiplatelets. This approach has not been widely tested yet and requires clinical validation.

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Commentary

The fact that yet another clinical case regarding the specified issue is controversial indicates the extreme urgency of the problem. Increasing number of patients receiving antiplatelet therapy, in addition to secondary prevention of vascular events, are exposed to the potential risk of increased bleeding at random (domestic) or planned trauma, which has already become a byword in the scientific literature. The case presented by the authors is even more confused by dual antiplatelet therapy in combination with thrombocytopenia in a patient with acute neurosurgery performed for absolute indications. The only positive thing can be the type of surgery: ventriculoperitoneal shunting, a typically less traumatic intervention with a low risk of bleeding. The team of neurosurgeons and anesthesiologists solved the problem by using an extended protocol of hemostasis testing having recoursed to antiplateletogram. Platelet hyperaggregation data as evidence of low sensitivity to dual antiplatelet therapy as well as the skill of neurosurgeons saved the patient from significant hemorrhagic complications. Despite the conciseness of the article, the authors managed to determine very accurately the options of interventions in this situation, while subjecting the efficacy of each of them to reasonable doubt.

In my opinion, the proposed article is very useful for practitioners, while its not entirely academic style endows it with a special charm and conveys the state of anxiety of neurosurgeons and anesthesiologists inevitably arising in a dramatic clinical situation.

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Evolution of Surgical Approaches to the Anterior and Middle Cranial Fossa: From Extended Craniotomy to the Supraorbital Keyhole Approach

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At the early stages of neurosurgery development, the use of extended craniotomy was dictated by poor illumination, inadequate visualization, and the lack of accurate diagnosis. Technological progress and the emergence of highly informative neuroimaging, microscopy, and neuroendoscopy techniques minimized neurosurgical approaches and, accordingly, approach-associated complications. At present, the fundamental philosophy of minimally invasive surgery is of particular topicality because this type of surgery contributes to rapid recovery of patients and reduces the period of hospital treatment. The aim of the article is to provide a brief historical overview of the evolution of surgical approaches to the skull base, ranging from extended craniotomy to minimally invasive interventions.

Keywords: history of surgical approaches, keyhole surgery, minimally invasive surgery.

At the early stages of neurosurgery development, surgical treatment of intracranial pathology involved extended craniotomy. Back when it was the only option. There were many reasons to perform extended trepanations: preoperative diagnosis often did not allow clear localization of pathology, lighting in an operating room was insufficient, and there were no special neurosurgical instruments. Therefore extended craniotomy was planned to search for underlying lesions. In addition, on average a surgical team consisted of three surgeons and one can imagine how difficult it was to navigate the surgical field [1, 2].

Subfrontal and transfrontal approaches were first described by J. Durante in 1884; the author used these approaches to resect olfactory meningioma. The postoperative period was uneventful, without any complications, and the patient was discharged home without neurological deficit [2].

The first description of the supraorbital subfrontal and transfrontal approaches was provided by F. Krause in 1908 (Fig. 1). In his book “Surgery of the Brain and Spine” Professor F. Krause presented two observations.

In the first patient, the subfrontal approach was used to remove a bullet from the area of the sella turcica. The surgery was performed 4 years after the injury. The access was lateral to the frontal sinus. F. Krause visualized the optic nerve and the carotid artery. The patient was discharged without neurological complications.

In the second patient, the surgery was performed for anterior cranial fossa meningioma. Remarkably, the operation was performed in two stages. The first stage included craniotomy, but the surgery was wrapped up due to brain edema and prolapse. The second stage was performed 3 weeks later in order to remove the tumor. F. Krause pointed out the need for significant traction of the brain by an assistant with two large spatulas (Fig. 2).

The opening of the dura mater was performed in the wings of the sphenoid bone. The tumor was removed by a finger, which later caused bleeding that was stopped by a tamponade.

Postoperatively, F. Krause remarked on later awakening of the patient, but there was no rough focal neurological deficit. However, the patient died later after suffering from disturbance of consciousness and respiratory disorders. Autopsy revealed hematoma in the resected tumor bed [3, 4].

In 1920, J. Tandler and E. Ranzi [5] also used subfrontal extradural approach to the pituitary gland. In 1912 and 1913, C. Frazier and L. McArthur [6, 7] modified the subfrontal approach by adding osteotomy of the superior border of the orbit (Fig. 3). Opening of the dura mater was performed at the level of the anterior clinoid process. According to C. Frazier, the expansion of craniotomy resulted in lesser traction of the frontal lobe and increase in surgical view of deep structures.

In 1916, H. Cushing performed the first total resection of tuberculum sellae meningioma using subfrontal approach. Surgeries were often divided into 2 or 3 stages due to onset of intraoperative edema, hemorrhage, and arterial hypotension. In 1938, H. Cushing and L. Eisenhardt [8] described their experience in the resection of 28 tumors in the book which has become seminal.

In 1920, G. Heuer [9] presented a series of patients who had pituitary tumors removed through subfrontal approach. The chiasmal area was accessed through extensive craniotomy in order to perform significant traction of the lobes (Fig. 4).

In addition to the complications associated with pituitary dysfunction, the authors identified complications associated with the traction of the brain in the form of epileptic seizures and rough neurological deficits. In two
patients, refractory intracranial hypertension in the postoperative period led to the death [9]. In 1922, W. Dandy [12] published the results of surgical treatment of meningiomas of the anterior cranial fossa, where he also used a fairly extensive craniotomy.

Inadequate lighting, lack of tools and accurate diagnosis forced neurosurgeons to resort to extensive approaches with significant traction of the brain tissue, endangering the lives of patients [10].

The first planned surgery, clipping of aneurysms, was performed on March 23, 1937 by W. Dandy [11, 12] (Fig. 5).

The clipping of the aneurysm of the mouth of the posterior communicating artery with a silver clip with preservation of the artery lumen was performed in a 43-year-old patient using frontal-lateral or so-called “pituitary” approach. In his surgery protocol, W. Dandy focuses on the significant relaxation of the brain after the opening of the chiasmal tank, which provided more room for manipulations. Interestingly, it was the first case where skin incision was performed within the scalp area.

The intervention was performed solely on the basis of clinical symptoms in the form of paresis of the oculomotor nerve, without angiography. By 1944 W. Dandy has accumulated considerable experience in operations for intracranial aneurysms, which he presented in his first monograph.

The most important step in the development of neurosurgery was the emergence and widespread use of microneurosurgical technique; one of the pioneers of its use was Yasargil. In 1975, M. Yasargil [16] modified W. Dandy’s “pituitary” approach. The pterional craniotomy differed in more basal resection of bone structures with resection of the lateral wing of the sphenoid bone.

In 1978 M. Brock et al. [17] described the experience of surgical treatment of aneurysms of the anterior circulation from the limited frontal-lateral approach. In 1982, J. Jane et al. [18] presented a description of the supraorbital approach in aneurysms and tumors of the suprasellar and orbital localization. Later J. Delashaw et al. [19, 20] modified this approach by using a technique which
Fig. 3. Subfrontalny access with osteotomy of the upper wall of the according to McArthur and Frazier.  

a — skin incision in subfrontal approach; b — abduction of osteo-aponeurotic flap to osteotomy line of the superior border of the orbit; c — retractor is installed in the frontal lobe, the eyeball was driven down, opening the dura mater was performed at the level of the wings of the sphenoid bone and the anterior clinoid process, the approach allows visualization of the chiasm and parasellar space [6].

Fig. 4. Surgical approach to tumors of chiasmosellar area.  

a — skin incision in subfrontal approach; b — traction of the brain; c — visualization of the optic chiasm after tumor resection [9].

involves breaking of the orbit’s roof or by supplementing craniotomy with temporal spread. R. Delfini [21] performed supraorbital craniotomy with a separate sawing off of the upper wall of the orbit. O. Al-Mefty et al. [22, 23] used supraorbital-pterional approach to access tumors of the skull base, supplementing it with osteotomy of the upper and lateral wall of the orbit. R. Smith et al. [24] described extended approach with pre-temporal spread for clipping aneurysms of the anterior circulation. J. Zabramski et al. [25] presented detailed description of technical features of orbitozygomatical approach and its advantages in the pathology of the anterior and middle cranial fossae. All these publications focused on the extended approach with more aggressive resection of the structures of the skull base. The main objectives of these approaches were to increase surgical view, reduce distance to pathological substrate and reduce traction injury by increasing bone corridor. However, soft tissue trauma, aggressive and widespread bone resection, and traction injury often resulted in postoperative complications that were not directly related to the purpose of the operation.

In 1998, E. van Lindert et al. [26] reported their experience in subfrontal supraorbital craniotomy through an incision on the eyebrows in the treatment of 197 aneurysms. In subsequent years there were publications on the use of supraorbital craniotomy through various skin incisions predominantly in aneurysms of the anterior circulation [27—29]. Despite different names and certain modifications, it is evident that all these types of approaches originate from the pioneering work of F. Krause [3]. F. Krause [3] understood the anatomical validity of subfrontal approach in which none of the structures, including the temporal pole, obstruct parasel-
lar space, providing the unique opportunity for free manipulations.

**Concept of keyhole-surgery**

A work by D. Wilson [30], published in 1971, became a defining one for development of principles of keyhole-surgery concept. D. Wilson based his research on the works of a famous surgeon, W. Halsted [31], who published his views on the need for improvements in surgical technique and minimizing aggressiveness of a surgery already back in 1924.

D. Wilson et al. begun to modify their technique in 1966 to match the requirements of microsurgery as the availability of the microscope allowed good visualization of deep structures through a small trepanation. D. Wilson used small linear cuts of the scalp, approximately 5—6 cm long, in different pathologies, including aneurysms, tumors, abscesses and other (Fig. 6).

Based on his experience D. Wilson made a number of conclusions: small trepanation is possible and in some cases is preferable: the approach is easier, faster and less traumatic compared to the classic and extended approaches, limited approach allowed minimization of tissue damage resulting in faster healing and minimal brain swelling. This technique gives a surgeon more time to focus on the immediate purpose of the surgery. The author performed over 100 craniotomies in which complications were rare and were quickly corrected. D. Wilson remarked that keyhole surgery is not a fetish, and that it requires careful assessment of intracranial pathology to select patients in whom this access can be used.

Axel Perneczky is undoubtedly the pioneer of the modern keyhole neurosurgery (Fig. 7). With his extensive experience, A. Perneczky promoted minimally invasive neurosurgery, formulated basic ideas of the keyhole concept and its capabilities in the modern world. Nowadays there is considerable experience in keyhole surgery which supports its effectiveness in minimizing aggressiveness of the surgery with proper selection of patients [32—38].

The main idea of the keyhole concept is to reduce tissue trauma. Long duration of craniotomy with retractor always imply certain damage to brain tissue from exposure to the environment that is non-physiological for the intracranial tissue: the influence of temperature, intense light from the microscope, solutions for irrigation, tampons, coagulation and so on.

Traction injury can lead to permanent neurological deficit, and, under certain circumstances, to development of large intracerebral hematomas with associated consequences. Various methods have been proposed to reduce traction injury, including certain types of anesthetic support, position of a patient on the operating table, and innovative retraction systems. However, the best traction is no traction. [36] Modern trends in neurosurgery rely on the use of dynamic traction, i.e. traction using tools in the hands of the surgeon, whether an aspirator or bipolar coagulator. Adequate anesthetic support, brain relaxation and proper choice of position of a patient on the operating table, using natural gravity, make it possible to create conditions for no-traction surgery.

Obviously, sometimes brain traction is unavoidable. However, neurosurgeon’s actions should be aimed at its minimization. Keyhole surgery significantly reduces duration of the surgery and creates conditions for minimizing the traction injury.

It is important to realize that convexally located lesions require craniotomy, which is at least slightly larger than the dimensions of a lesion. In common arteriovenous malformations (AVM) the access should be wide enough to visualize the AVM afferents and draining veins. On the contrary, keyhole approaches can be used in case of deep lesions [39—41].

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**Fig. 5.** The first ‘pituitary’ approach according to W. Dandy to aneurysm of the interior carotid artery.

a — the patient’s appearance before the surgery; b — the volume of pituitary access, according to cranigraphy, clip is visible (indicated by arrows); c — appearance of the patient 12 days after the surgery. Significant regression of paresis of the oculomotor nerve is evident [11].
Conclusion

The philosophy of minimally invasive surgery is gaining particular relevance nowadays, since in most cases neuroimaging provides comprehensive information about the nature and localization of pathology, while modern surgical equipment allows properly trained surgeon to operate through a “keyhole”. Surgical intervention must be performed with a minimum of iatrogenic complications and must achieve maximum efficiency.

Keyhole concept is obviously an innovative direction in neurosurgery. As a part of the evolutionary process in surgery, modern conditions, including availability of endoscopic assistance, microscope-associated options such as angiography and fluorescent staining of tumor tissue, intraoperative neurophysiological methods of control and capabilities of modern neuroanesthesiology, allow minimally invasive interventions to significantly reduce the invasiveness of surgical approaches, approach-associated complications and adverse cosmetic effects. Rapid recovery of patients, shorter hospital treatment and the fastest possible recovery of social and labor adaptation after complex neurosurgical interventions are the priority today.

It must be emphasized that the keyhole approaches should not be an end in itself. Prerequisites for their use include careful selection of patients for such interventions, taking into account the size and nature of pathological lesion, condition of the surrounding brain tissue and projected surgical complications.

Authors declare no conflict of interest.
Commentary

The authors present a consistent historical analysis of the evolution of subfrontal approaches from extended craniotomy to minimally invasive interventions. Minimization of craniotomy to access a basal pathology was a natural process and a consequence of the emergence of highly informative diagnosis of intracranial pathology, improvement in microneurosurgical techniques, intraoperative visualization, neuroanesthesiology and neuroreanimation. Nowadays, a neurosurgeon should have a mastery of different techniques for approaching to lesions of the skull base and should not use a single universal approach, regardless of the location and size of lesion. On the other hand, the choice of keyhole approach can not be regarded as universal, and selection of candidates for such interventions must be balanced and on case by case basis, so as not to jeopardize the patient’s life.

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Epidemiology, Diagnosis, Clinical Symptoms, and Classification of Primary Malignant Skull Base Tumors

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Literature review presents up-to-date information on the prevalence, incidence, clinical manifestations, diagnosis, and classification of primary malignant skull base tumors (PMSBTs). In the structure of total cancer incidence, malignant head and neck tumors account for 5% of all annual cancer deaths in the USA and are among the 5 most common groups of tumors in males worldwide. These tumors most often develop during the sixth decade of life and occur 2 times more often in males than in females. In Russia, the incidence of PMSBTs (as of 2012) was 0.62% out of all newly diagnosed malignant tumors. The incidence rate amounts to 0.66 per 100,000 population and is significantly higher than the global rate (0.44 per 100,000). About a half of all malignant skull base tumors are epithelial in origin and involve the anterior parts of the skull base. Squamous cell carcinoma, adenocarcinoma, and non-Hodgkin’s B-cell lymphoma are the most common histological types of malignant skull base tumors. Treatment of skull base tumors is an interdisciplinary problem, being the area of interest of otolaryngologists, dentists, ophthalmologists, neurosurgeons, plastic surgeons, radiologists, and chemotherapists. Physical and endoscopic examinations, endoscopic transnasal biopsy, CT, MRI, PET/CT, and ultrasound are typically used for verification of the diagnosis, tumor staging, and selection of treatment approach. The review describes the criteria for TNM staging of malignant tumors of the nasal cavity and paranasal sinuses in accordance with the 7th version of the TNM recommendations of the American Joint Committee on Cancer (AJCC). The TNM-based staging depends on the location (maxillary sinus, nasal cavity, or ethmoidal labyrinth) and histological structure of the tumor, which, in turn, determines the tactics of comprehensive treatment and a prognosis group.

**Keywords**: skull base, oncology, malignant tumor, prevalence, diagnosis

### Epidemiology

In the structure of total cancer incidence, malignant head and neck tumors account for 5% of all annual cancer deaths in the USA. These malignant tumors are among the 5 most common tumors in males worldwide and they are 6–7th most common among all malignant tumors [1]. According to the literature, 5-year survival rate of patients with head and neck cancer, who receive adequate complex treatment, is 80%. The median age at the time of diagnosis of squamous cell carcinoma of the head and neck is about 60 years, but the incidence of the disease in middle-aged persons (under 45 years) increases, which is probably due to the spread of human papillomavirus (HPV) [2].

The publications on head and neck tumors invading the skull base are scarce. [3] It should be noted that skull base tumors are diverse in their morphological structure and localization. Epithelial cancers originating from the paranasal sinuses are the most common ones and they are difficult to differentiate from the tumors of the superior nasopharynx. Morphologically, these tumors can be very similar, but they are fundamentally different in treatment and outcomes of the disease. In addition, head and neck tumors can originate from bone and cartilaginous tissue. Usually these tumors are malignant and capable of metastasis.

Tumor invasion can be intracranial, destroying skull base bones or extending through the natural forams (perineurally), involving several anatomical zones, which results in injury to the functionally important skull base structures. Tumor invasion to the external skull base, infratemporal and pterygopalatine fossae, and orbit in combination with intracranial growth requires concerted action of oncologists and neurosurgeons, as well as radiologists and chemotherapeutists [4].

About a half of all malignant skull base tumors are epithelial and involve the anterior skull base [5]. The vast majority of these tumors develop from the mucous membrane of the nasal cavity and paranasal sinuses.

Malignant tumors of the paranasal sinuses, affecting the skull base, account for 0.2% of all malignant tumors and 3–5% of malignant neoplasms of the upper respiratory tract. Maxillary sinus and nasal mucosa are the most common source of these tumors. Most often, they occur during the sixth decade of life; they are 2 times more common in males than in females. According to the most recent data, the incidence increases in males [6] due to HPV and other carcinogenic factors. Thus, formaldehyde significantly increases the risk of squamous cell carcinoma and adenocarcinoma. Mustard gas, asbestos, nickel, and radium and cause the development of squamous cell carcinoma, while wood dust and leather working predispose to adenocarcinoma [7]. It has been proved that HPV have an influence on malignization of the process in cases of inverted papilloma and squamous cell carcinoma [8]. It is also known that HPV-induced
squamous cell carcinoma of the paranasal sinuses has a better prognosis compared to other forms [9].

In Russian Federation, the incidence of malignant tumors of the nasal cavity, paranasal sinuses, nasopharynx, and the middle ear accounts for 0.54% of all newly diagnosed cancers as of 2012. The incidence in 2 times higher in males than in females and the overall incidence rate is 0.66 cases per 100,000 population, far exceeding the global level (0.44 per 100,000) [10].

In 46% of cases, tumors originate in the nasal cavity, 33% — maxillary sinus; other sites account for 20%. The most common histological types: squamous cell carcinoma — 42%; non-Hodgkin’s B-cell lymphoma — 11%; adenocarcinoma — 10%. When the initial tumor growth occurs in the nasal cavity, the early emergence of airway obstruction symptoms enables early diagnosis, which is reflected in the statistics of TNM distribution. Thus, the occurrence of T1 and T4 tumors of the nasal cavity is 44.9 and 22.5%, respectively. Tumors growth in the paranasal sinuses is asymptomatic for a long period of time, and therefore it is most often detected at the later stages: the incidence of T1 and T4 tumors of the paranasal sinuses is 10 and 55%, respectively. The same regularity is observed in the disease stages: stage IV tumors of the nasal cavity account for 21%, while stage IV tumors of the paranasal sinuses on average account for 52%. At the time of the diagnosis, tumors typically have neither regional, nor distant metastases. For example, regional metastasis is observed on the average in 20% of cases, while distant metastasis is observed only in 10% of cases. The overall 5-year survival of patients with malignant tumors of the nasal cavity and paranasal sinuses who receive combination therapy is 55.8%. It is higher in the case of nasal cavity tumors (68%) compared to tumors of the paranasal sinuses (42 to 48%). Adenocarcinoma is the most favorable histological option in terms of the overall 5-year survival (63.7%) among the most common epithelial cancers, followed by squamous cell carcinoma (53%), and all other epithelial tumors (37.8%) [11].

Currently, according to the National Institutes of Health (USA), more than 900 active clinical trials for malignant neoplasms with this location are carried out. However, no definite algorithm of diagnosis and treatment has been developed. For example, patients with basilar sinus cancer are excluded from the vast majority of these studies.

In Russian Federation, there is no consistent approach to treatment of this disease either. The capacity and quality of medical care largely depend on protocols adopted in the clinic, where the patient receives treatment. Patients with severe intradural proliferation of the process and signs of intracranial hypertension are usually considered to be inoperable and are sent to palliative care specialists. The data on patients with this pathology are not recorded. Despite the current development of information technology, we should mention that there is no website dealing with this issue, which could be used for information, education, communication between specialists, and qualified answers to patients’ questions.

During the period from 2000 to 2015, 9 research on this issue were carried out in Russian Federation, including 3 studies at the Burdenko Neurosurgical Institute [12–14]; 2 studies at the Blokhin Russian Cancer Research Center (Moscow, Russia) [15, 16]; one study at the prof. Polenov Russian Research Neurosurgical Institute (St. Petersburg) [17], Northern State Medical University (Arkhangelsk) [18], Medical Radiological Research Center of the Russian Academy of Medical Sciences (Obninsk) [19], and Institute of Advanced Training of the Federal Medical and Biological Agency (Moscow, Russia) [20].

These studies mainly focus on surgical aspects of treatment of patients with malignant skull base tumors, as well as the issues of chemotherapy and radiation therapy for tumors without intracranial growth.

**Nosological forms of primary malignant skull base tumors**

Primary malignant skull base tumors (PMSBTs) are the heterogeneous group of tumors due to the wide variety of tissues located at this anatomically complex area. Patients with intracranial tumor invasion need both oncological and neurosurgical care. In some cases, the latter should be urgent, when there are signs of intracranial hypertension and herniation. The transformation to the squamous form of head and neck tissue cancer is the final point of the transformation process from normal epithelium to hyperplasia, dysplasia, carcinoma in situ, and finally invasive carcinoma [21]. Partial chromosome damage is associated with different stages of tumor development. Major genetic changes, including loss of heterozygosity of certain chromosomes (3p14, 9p21, 17p13, 8p6p, 4q27, and 10q23), as well as increased expression, removal, increased or reduced regulation of certain oncogenes or tumor suppressors, including endothelial growth factor receptors (EGFR), p53, Rb, p65, cyclooxygenase 2 (COX-2), p16, cyclin D1, and phosphatase, an angiotensin homolog (PTEN), are specific for each pathological stage of the disease [21].

The main histological groups of the primary sinonasal malignant tumors are characterized by pronounced diversity and are described in the WHO classification [22].

1. **Epithelial tumors**
   - Squamous cell carcinoma (carcinoma),
   - Adenocarcinoma
   - Salivary gland tumors
   - Sinonasal undifferentiated carcinoma (sino-nasalis undifferent carcino, SNUC)
2. **Neuroectodermal tumors**
   - Esthesioneuroblastoma
   - Melanoma
3. Neuroendocrine tumors
   • Sinonasal neuroendocrine carcinoma — SNEC)
4. Malignant nerve tumors
   • Malignant peripheral nerve sheath tumor
5. Bone and chondroid sarcomas
6. Soft tissue sarcoma
7. Hematogenous and lymphogenous tumors
8. Germinative-cell tumors

Clinical presentation of the skull base cancer process

Identification and adequate strategy for PMSBTs are the important aspects that have major impact on clinical outcomes, particularly survival rates [23]. Since the stage (degree) of the disease is the most important prognostic factor in treatment of skull base cancer, early identification and treatment of small tumors at the initial stages correlate with better survival prognosis. Neurological symptoms are determined by topographical location of the skull base tumor and mainly manifest as syndromes associated with impairment of cranial nerves I–VI.

Greenberg et al. [24] identified several syndromes according to clinical and neurological symptoms. For example, tumor invasion to the orbit results in clinical manifestation in the form of orbital syndrome [25]; tumor located at the middle cranial fossa results in sellar and parasellar syndromes, syndrome of petrous pyramid and trigeminal ganglion impairment. In addition, there is tumor invasion to the nasal cavity and paranasal sinuses. Malignant tumors growing from the nasal mucosa cause long-term unilateral nasal obstruction, dysphonia, and nasal bleeding episodes. Local cephalalgia, impaired function of the primary olfactory structures (hypo- or anosmia) are also characteristic of these tumors. Chronic unilateral serous otitis media may be due to nasopharyngeal cancer, blocking the Eustachian tube. Maxillary sinus tumors can manifest in the form of teeth loss and lockjaw. Tumors growing from the mucous membrane of the paranasal sinuses cause the symptoms similar to chronic sinusitis. Tumors invading the orbit can manifest as diplopia, ptosis, exophthalmos, and eye movement disorders. Involvement of the lacrimal apparatus results in scleral dryness and trophic eye disorders. Compression of the optic nerve in its canal results in decreased visual acuity and visual field loss [26]. Tumor invasion to the superior orbital fissure and anterior cavernous sinus results in facial hypesthesia and oculomotor disorders. Destruction of the base of the anterior cranial fossa and invasion to the base of the frontal lobes result in cognitive and mnestic disorders, personality disorders, and intracranial hypertension signs [27, 28].

CT and endoscopic examination of the nasal cavity can reveal unilateral polypoid formations. For a long time, these patients are followed by otolaryngologists, dentists, and ophthalmologists, until the protracted disease or development of neurological symptoms requires CT, MRI, and consultation of neurosurgeon and oncologist. Timely axial CT and endoscopic transnasal biopsy of the neoplasm that is suspected to be malignant are the key to early diagnosis and successful treatment of PMSBTs. Rapid progression of symptoms can be indicative of the malignant process. A history of malignant tumors in other systems and organs is indicative of the possible metastatic character. In other cases, the primary tumor should be suspected. In the case of body weight deficit and its rapid progression, malignant process should be suspected. Palpation of cervical, supraclavicular, and axillary lymph nodes may indicate the presence of regional metastases [29].

Patient examination

When tumor is suspected, physical examination of the patient should be followed by contrast-enhanced MRI and CT of the brain. These types of neuroimaging enable determining the presence and spread of neoplastic lesion, detecting signs of intracranial hypertension and tumor invasion to the dura mater and brain tissue, and suggesting histological diagnosis and the possibility of endoscopic biopsy.

Histological verification of the process is then carried out. The presence of accessible portion of the tumor in the inferior and medial nasal meatus enables biopsy under local anesthesia. When the tumor is located in the paranasal sinuses, superior nasal passage, and ethmoidal bone structures, biopsy should be conducted under general anesthesia. In some situations, histological diagnosis immediately shows primary or metastatic nature of the tumor. For example, esthesioneuroblastoma is a primary malignant tumor of the olfactory epithelium and the presence of kidney cancer cells in samples is indicative of metastatic nature of the lesion. In other

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cases, such as squamous cell carcinoma, the primary site can be located either at the site of biopsy, or other site located in other organs. Currently, immunohistochemical examination facilitates detection of the primary site.

In all cases, where the malignant nature of the tumor was confirmed, cancer screening is indicated to identify the primary tumor (if any) and search for regional and distant metastases [16, 30, 31]. Ultrasound of the cervical lymph nodes and supraclavicular region is required to determine the stage of the disease and to develop the correct treatment tactics. If enlarged lymph nodes have been detected, ultrasound-guided one-step biopsy should be carried out.

It should be noted that the search for regional metastases is mandatory only in the case of epithelial origin of a malignant tumor. Regional metastasis is not typical and very rare in the case bone or soft tissue sarcoma. For this reason, examination of regional lymph nodes in these patients is carried out only if enlargement of these nodes is detected during physical examination [31]. If metastases are detected in cervical lymph nodes, contrast-enhanced MRI of the neck is required. Ultrasound of the internal organs and pelvic organs, as well as CT of the chest is indicated, when searching for distant metastases. It should be noted that in the case of bone and soft tissue sarcomas, only lung CT is required, as metastasis in other organs is not typical.

Whole-body Positron Emission Tomography (PET) with glucose is a highly sensitive and specific (up to 90%) method to detect possible metastases in the lymph nodes, skeletal bones, and internal organs and to assess disease staging. PET also contributes to the discovery of latent local primary disease. In our diagnostic algorithm, PET was optional, because it is cost-consuming and not routine used in Russia.

Thus, examination of PMSBT patients must include at least the following studies:
- history taking;
- physical examination;
- endoscopic ENT examination (if necessary);
- contrast-enhanced MRI and CT of the head;
- dental examination;
- ultrasound of the cervical lymph nodes and supraclavicular region;
- biopsy of the lymph node, if it is larger than 3 cm in diameter;
- MRI of the neck, if metastasis is detected in cervical lymph node;
- CT scan of the chest,
- PET-CT with glucose.

**Principles of staging of anterior skull base tumors**
First classification of the anterior skull base tumors divided tumors based on their location with respect to

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**Fig. 1.** Schematic representation of tumor growth in the paranasal sinuses and nasal cavity (T1 and T2, TNM classification, 10th edition).

**Fig. 2.** Schematic representation of tumor growth in the paranasal sinuses and nasal cavity (T3, TNM classification, 10th edition).
the Ohngren’s line (from the mandibular angle to the medial corner of the ipsilateral eye). Tumors located below this line were considered as resectable [32].

Current TNM-based staging criteria for malignant tumors that occur in the superior airways, paranasal sinuses, and salivary glands, have been developed by the American Joint Committee on Cancer (AJCC) [31]. The criteria are regularly reviewed and updated. To date, the 7th version of TNM (2010) is the most recent one. Stage groups used for head and neck cancer are based on the following notation: T (primary tumor), N (regional lymph node), and M (distant metastasis).

Due to changes in growth, behavior, prognosis, localization, and distribution of head and neck cancer, there are differences in staging criteria for each anatomical location and histological structure and this will change the respective tactics of complex treatment.

Fig. 3. Schematic representation of tumor growth in the paranasal sinuses and nasal cavity (T4a, TNM classification, 10th edition).

Fig. 4. Schematic representation of tumor growth in the paranasal sinuses and nasal cavity (T4b, TNM classification, 10th edition).

The following staging principles were suggested for tumors originating from the maxillary sinus, nasal cavity, and ethmoidal labyrinth:

**Primary tumor (T)**
- TX — primary tumor can not be assessed
- T0 — no evidence of primary tumor
- Tis — in situ cancer

**Maxillary sinus**
- T1 — tumor is bounded by mucosa without bone destruction.
- T2 — tumor, causing bone destruction with proliferation to the hard palate and/or medial nasal meatus except for spread beyond the posterior wall of the maxillary sinus and the wings of the sphenoid bone (Fig. 1)
- T3 — tumor, involving any of the following: the posterior wall of the maxillary sinus, subcutaneous soft
tissue, inferior or medial orbital wall, pterygoid-fossa, ethmoidal labyrinth (Fig. 2).

T4a — moderately locally advanced tumor. The tumor involves the anterior orbital complex, skin of the cheek, wings of the sphenoid bone, infratemporal fossa, perforated plate, basilar sinus, or ethmoidal labyrinth.

T4b — severe locally advanced tumor. The tumor that involves any of the following structures: the roof of the orbit, dura mater, brain tissue, middle cranial fossa, cranial nerves, other than maxillary nerve, nasopharynx, or clivus.

Nasal cavity and ethmoidal labyrinth

T1 — unilateral tumor bounded by the ethmoidal labyrinth with/without invasion to bone structures

T2 — ethmoidal labyrinth and nasal cavity tumor with/without invasion to bone structures.

T3 — tumor that involves medial or inferior wall of the orbit, cheek skin, wings of the sphenoid bone, maxillary sinus, palate, or perforated plate (Fig. 3).

T4a — moderately locally advanced tumor. Tumor that involves any of the following: anterior orbital complex, skin of the nose or cheeks, anterior cranial fossa, wings of the sphenoid bone, basilar or maxillary sinus.

T4b — severe locally advanced tumor. The tumor that involves any of the following: the roof of the orbit, dura mater, brain tissue, middle cranial fossa, cranial nerves other than maxillary nerve, nasopharynx, or clivus (Fig. 4).

The main criteria to assess the stage of nasal cavity and paranasal sinus cancer according to the TNM

NX — regional lymph nodes can not be assessed

N0 — there is no evidence of metastases to the regional lymph nodes

N1 — metastasis to an ipsilateral lymph node no larger than 3 cm

N2 — metastasis to an ipsilateral lymph node larger than 3 cm but no larger than 6 cm

N2c — bilateral or contralateral multiple metastases in the lymph nodes no larger than 6 cm each

N3 — metastasis to a lymph node larger than 6 cm (Fig. 5).
Distant metastases
M0 — no distant metastases detected.
M1 — distant metastases are detected.

Conclusion
Management of PMSBT patients requires an interdisciplinary approach to treatment involving surgical oncologists who deal with head and neck tumors, ENT surgeons, neurosurgeons, and, in some cases, maxillofacial and plastic surgeons, as well as radiooncologists, radiologists, and chemotherapeutists. There is no clear guidance on the management of this particular group of patients in the world. However, the data presented in this review demonstrate relatively high survival rates, and therefore proves the relevance of the efforts to develop algorithms for complex treatment of PMSBT patients. The development of the optimal methods of examination and complex treatment for patients with malignant skull base tumors should improve the results of surgical treatment (increase its radicality and reduce the number of complications), as well as improve disease outcomes in general by increasing the terms of disease-free survival using the complex treatment. It will also enable more extensive use of various treatments for these patients in the neurosurgical practice and reduce the time of treatment and rehabilitation, reducing the rate of disability and improving functional outcomes of treatment.

Authors declare no conflict of interest.

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Neuroendocrine dysfunction, in particular, impaired synthesis of anterior pituitary hormones, is a common complication of traumatic brain injury. Deficiency of tropic pituitary hormones entails a hypofunction of the related peripheral endocrine glands and can be accompanied by persistent endocrine and metabolic disorders. In particular, the hypophyseal mechanisms are the key ones in implementation of most stress effects. Adequate implementation of these mechanisms largely determines a favorable outcome in the acute stage of disease. Traumatic brain injury (as well as any significant injury) initiates a stress response that cannot develop in full in the case of pituitary gland failure. It is logical to suppose that the course of the acute phase of stress in the presence of hypopituitarism is different to a certain extent from the typical course, which inevitably affects certain adaptation elements. In this review, we analyzed the adaptive effects of stress after traumatic brain injury.

**Keywords:** hypothalamic-pituitary system, neuroendocrine dysfunction, hypopituitarism, traumatic brain injury, stress response, adaptation.

Endocrine dysfunction following traumatic brain injury (TBI) is the focus of constant attention of health professionals dealing with brain injury [1—11]. Trauma leads to impaired synthesis of anterior pituitary hormones and this results in hypofunction of the related peripheral endocrine glands [4—11]. Most of the authors discuss the probability of injury to either endocrine axes, metabolic manifestations of different types of hypopituitarism, the prospects for normal function recovery, and the effectiveness of replacement therapy [4—13].

At the same time, any significant trauma stimulates a complex of neuroendocrine metabolic reactions characteristic of critical illnesses of various origins that are subject to common laws of stress [14—28]. Afferent impulses arising due to tissue damage activate a complex of the hypothalamic-pituitary structures to integrate metabolic effects of stress [14—16, 19, 27]. This integrated non-specific response to injury commonly covers all the pituitary mechanisms and is almost always adaptive in the acute stage [14—16, 19, 26, 27].

The sympathetic-adrenal and pituitary-adrenal systems are believed to be the major effectors of stress. These systems are associated with basic physiological responses that provide immediate adaptation: an increase in cardiac output and heart rate, systemic blood pressure, relaxation of bronchial smooth muscles and activation of external respiration, acceleration of nerve impulse travel, and an increased tonus of non-specific activity of the central nervous system [14, 15, 19, 28].

However, the adaptive response is not centered on the activation of the vital functions. Stress reaction not only stimulates the activity of basic vital systems, but also intensifies their activity. Thus, stress reaction necessarily involves increased bioavailability levels of energy metabolism substrates — glucose, fatty acids, amino acids, ketones, and also optimization of tissue metabolism. On the one hand, this effect is achieved via mobilization of energy resources, and on the other hand, by limiting energy resource consumption at the periphery, in the organs that are not directly involved in ensuring vital functions (Figure). Thus, the nerve tissue, cardiovascular and immune systems, and blood cells receive large amounts of metabolic substrates [5, 14, 15, 20, 23, 29].

Mobilization of energy resources is primarily implemented in stress hyperglycemia that results from combined action of several so-called contra-insular hormones. The concentration of glucose in the blood begins to rise during the first hours after the onset of acute stress under the influence of catecholamines and glucagon that stimulate glycogenolysis in the liver and muscles [14, 16, 19, 27]. Glucagon is released slightly later than catecholamines and repeats and amplifies the effect of catecholamines. However, glycogen stores become depleted rather fast under stress — within a few hours [30]. At this stage, hyperglycemia needs to be maintained by additional glucose synthesis; gluconeogenesis enzymes in the liver stimulate glucagon and glucocorticoids. Glucocorticoids also provide a contra-insular effect, similar to the growth hormone, whose secretion also increases. The synthesis of insulin reduces. Cytokines (tumor necrosis factor-α, interleukins) at elevated production in response to injury and due to specific stress mechanisms maintain insulin resistance of tissue and enhance contra-insular hormone synthesis [16, 19, 26, 27, 29, 31].

Simultaneously, lipid mobilization takes place. Activation of lipases in adipose tissue, skeletal muscle and heart occurs under the influence of catecholamines, glucagon, cortisol, growth hormone, and perhaps, cytokines [16, 19, 20, 29, 31]. Meanwhile, similarly in terms of blood glucose, catecholamines and glucagon provide a quick and short-term effect, and cortisol and somatotropin (growth hormone) is responsible for a
longer effect. This results in an increased serum concentrations of triglyceride hydrolysis products — free fatty acids and glycerol [11, 16, 29, 30].

Amino acids that are formed after protein catabolism of skeletal muscle and loose connective tissues under the influence of cortisol may also act as energy metabolism substrates [19, 27].

Thus, the growth hormone and cortisol have a leading role in the mobilization of energy resources (Figure).

Limitation of metabolic processes at the periphery is achieved through lower synthesis of gonadotropic hormones (luteinizing (LH) and follicle stimulating hormones) and thyroid stimulating hormone (TSH), which is accompanied by reduced activity of the related endocrine glands and target organs [20, 23, 27]. These effects are consistent with the features of the somatotropin axis function under stress. Thus, under normal conditions, glucose and fatty acid release under the influence of somatotropin increases circulating levels of IGF-1 (IGF-1). Therefore, the available substrates are “captured” by anabolic processes, whose inducer is IGF-1. In contrast, the synthesis of IGF-1 is suppressed under stress (presumably due to proinflammatory cytokines) [20, 22, 23]. As seen, blood glucose is mainly delivered to insulin-independent tissues: in the first place, to neurons and blood cells; fatty acids are metabolic substrates for the myocardium, kidney and liver, as well as an important gluconeogenesis substrate [15, 16, 22, 27].

Amino acids, products of protein catabolism, on the one hand, can enter gluconeogenesis or be metabolized to fatty acids and, one the other hand, serve as substrates for the synthesis of acute-phase proteins in the liver [14, 19, 26]. Somatotropin axis function under stress is also mostly centered on delivery of energy resources to provide vital functions.

Thus, multi-sided and harmony adaptive effect of energy metabolism optimization under acute stress is achieved by the complex reaction of all endocrine systems originating in the anterior pituitary cells (and not only in the pituitary-adrenal axis).

In hypopituitarism, even partial, such harmony will definitely be violated.

TBI is a leading cause of hypopituitarism [5—9, 11]. Damage to different nuclei of the anterior pituitary occurs in 25—50% of cases after trauma (the data are vary substantially depending on the assessment method of hormone deficiency with no consensus on this issue). Injury to the pituitary gland is believed to be polyepticologic, and in addition to direct trauma this may include hemorrhagic or ischemic mechanisms, elements of inflammation and autoimmune processes; genetic predisposition also plays an important role. Researches fail to establish the correlation between the severity of TBI and the probability of hypopituitarism development [4, 5, 7—11].

Anyway, injury to different nuclei of the anterior pituitary gland is accompanied by impaired secretion of the related hormones at the periphery; this is the pathway how deficiency develops in one or several and rarely simultaneously in all endocrine axes [4—11]. As a result, adaptive reactions at the acute stress stage cannot develop in full. It is logical to assume that processes of energy metabolism optimization are the first to suffer due to impaired synthesis of the pituitary-adrenal axis hormones and the growth hormone. According to the literature
data, traumatic injury is quite frequent in these systems — up to 1/3 of all cases of acute disorders (data vary substantially depending on the method of estimating failure of a particular system) [5, 6]. Synthesis of cortisol can also be maintained in the absence of adrenocorticotropin hormone through the direct influence of catecholamines and cytokines on the cells of the zona fasciculata of the adrenal cortex [34, 35], but whether this alternative pathway of cortisol synthesis regulation provide adequate adaptation remains unknown. As a result, energy resource deficit can develop immediately after extinction of the effects of "short-acting" hormones. The fact that this condition can be considered similar to the "wasting syndrome", which is more characteristic of chronic stress, cannot be ruled out [20, 22, 23].

It is more difficult to interpret the condition of endocrine systems, wherein the level of hormones under stress and trauma-induced hypopituitarism undergo similar changes. These include a decreased secretion of thyroid and reproductive hormones, as well as an increased secretion of prolactin [4—6, 32]. At first sight, it may seem that hypopituitarism does not allow to develop stress response in full, but only aggravates the effects of stress.

This postulation is probably reasonable for the thyroid axis hormones. Indeed, inhibition of thyroid function in the early stages of the stress response is difficult to distinguish from impaired synthesis of TSH due to TBI [5, 6, 21]. However, quite definite differences between these conditions can be traced in sex steroids. Thus, general cases of critical illness hypogonadism develop due to decreased LH release frequency. TBI-associated hypogonadism may involve decreased LH release amplitude, but not release frequency [5]. In traumatic tissue injury, cytokines can suppresses testosterone synthesis at the level of the Leydig cells, bypassing the pituitary mechanisms [5].

In addition, estradiol is known to have neuroprotective effects. Testosterone after conversion to estradiol can also have the same effect [5]. Estrogens have the capacity to block the release of inflammatory mediators such as nitric oxide, prostaglandin E2, matrix metalloproteinase-9, and also receptors for complement component 3. Androgens exert a systemic anabolic effect. Thus, it seems that in TBI, which is not complicated by hypopituitarism, sex steroids could act as neuroprotective agents. One cannot exclude that suppression of the gonadotropic axis in injury of the pituitary gland reduces reparative and compensatory resources at other parts of the injured brain.

Thus, events of post-traumatic hypopituitarism may be expected to significantly limit the implementation of adaptive stress effects. It is most likely that the processes that will suffer are as follows:

— Mobilization of energy metabolism substrates and their redistribution in the body; moreover, energy resources most likely will not be delivered to the vital organs, first of all, to the injured brain tissue, at the extent that is necessary for full recovery;

— Implementation of neuroprotective effects of steroids.

Neuroendocrine pathology after TBI has not been considered in scientific medical literature from this point of view. We see important to attract attention of health practitioners to the failure of the listed adaptation mechanisms. An in-depth study of these processes followed by the application of these results in clinical practice could probably contribute to both decline in general complication frequency and more effective recovery of brain activity after TBI.

Authors declare no conflict of interest.

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**Commentary**

This review paper is of interest in different aspects. Firstly, the work continues the traditional line of research carried out at the Burdenko Neurosurgical Institute dedicated to fundamental issues of impaired hormonal status in patients with brain injuries and diseases.

Secondly, the authors did not limit themselves to the analysis of the literature data and afforded an opportunity to provide an interesting interpretation of the data. In particular, the idea to give a comparative description of hormonal changes in traumatic injuries in general and isolated brain injury seems attractive. The authors succeeded in finding both similarities and fundamental differences between these pathological conditions. This position made it possible to offer promising therapeutic approaches aimed at correcting reproductive hormone levels as a means to improve the reparative processes in the brain.

This article is of great interest for the readers of this journal.

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