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In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the N.N. Burdenko Journal of Neurosurgery was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.
Renal cell cancer comprises 85% of all malignant tumors in the urinary system; in 2–17% of patients, it is followed by metastatic brain lesions [9]. The development of brain metastases results in neurological and mental disorders, as well as rapid disability of patients [11, 14, 21, 24, 27, 30].

Intracranial metastases are one of the mechanisms of hematogenous dissemination of renal-cell cancer that can be revealed within several years after nephrectomy. In approximately 90% of patients with metastatic brain lesions, a primary focus has already been diagnosed, while in 8–10% of the patients, symptoms of intracranial metastases are the first signs of renal cancer [34].

According to the literature [2–7, 10, 13, 15–17, 20, 22, 23, 25, 28, 29, 31, 33, 35–38], the median lifetime in patients with brain metastases from renal-cell cancer is 4–14 months. Nephrectomy, Karnofsky performance status of a patient, absence of extracranial metastases, and marginal dose per the largest metastasis more than 20 Gy. RS is one of the basic treatment methods for the pathology under discussion. The method is highly efficient with reference to control of a tumor growth and a patient’s quality of life. It is noteworthy that patient’s lifetime depends on the completeness of the complex treatment of primary disease and its success.

Keywords: radiosurgery, Gamma Knife, renal-cell cancer, intracranial metastases.
Material and Methods

Characteristics of patients

A total of 312 patients with brain metastases from renal-cell cancer were treated using a Gamma Knife at the Department of Stereotactic Neurosurgery and Radiology at Homolka Hospital (Prague, Czech Republic), Radiosurgical Center of the International Institute of Biological Systems (St. Petersburg, Russia), and Stereotactic Radiosurgery Gamma Knife Center (N.N. Burdenko Neurosurgical Institute, Moscow, Russia) since February 2000 through October 2009. The mean age of the patients was 61 years (range: 32–86 years); the gender ratio was 92 (29%) females and 220 (71%) males. Single metastases were detected in 136 patients (43%); 2–4 metastases, in 149 patients (48%); and multiple metastases (≥5), in 27 patients (9%). The median interval between the diagnosis of a primary tumor and detection of metastases in the brain was 17 months (range: 0–228 months).

In 264 patients (85%), the primary tumors had been removed (nephrectomy) before the intracranial metastases were detected, while in 63 patients (20%), the tumors were progressing. Metastases to the other organs, besides brain metastases, were detected in 200 patients (64%).

GK STS was preceded by total brain irradiation (mean dose of 30 Gy, 9–20 fractions) in 10 patients (3%), while in 54 patients (17%), GK STS was preceded by open neurosurgical tumor resection. MRI detected metastatic hemorrhages in 67 patients (21%). Patients’ performance status at the first session was evaluated according to the Karnofsky scale; its median value was 80% (50–100%) (Table 1).

 Characteristics of radiosurgical treatment

A stereotactic surgery device, Leksell Gamma Knife model C/4C (ELEKTA AB, Sweden), was used for treatment.

A Leksell stereotactic frame was fixed at a patient’s head under local anesthesia. Contrast-enhanced MRI scanning in modes providing sections thinner than 1–2 mm was performed.

The irradiation was planned according to the marginal isodose of 20–92% (median 50%). An average prescribed dose was 20 Gy (10–27.6 Gy). The median volume of the largest tumors was 5.6 cm³ (Table 2).

The further management of a patient involved routine (once per 3–5 months) follow-up of the brain using contrast-enhanced MRI. In case of impairment of the neurologic status, its cause was determined using unscheduled

Table 1. Characteristics of the patients with renal-cell cancer metastases to the brain (n=312)

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>abs.</td>
</tr>
<tr>
<td>Males</td>
<td>220</td>
</tr>
<tr>
<td>Females</td>
<td>92</td>
</tr>
<tr>
<td>Number of metastases:</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>136</td>
</tr>
<tr>
<td>2–4</td>
<td>149</td>
</tr>
<tr>
<td>≥5</td>
<td>27</td>
</tr>
<tr>
<td>Whole brain radiotherapy (WBRT)</td>
<td>10</td>
</tr>
<tr>
<td>Resection of one or several metastases</td>
<td>54</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>264</td>
</tr>
<tr>
<td>Metastases to the other organs</td>
<td>200</td>
</tr>
<tr>
<td>Localization of intracranial metastases:</td>
<td></td>
</tr>
<tr>
<td>frontal area</td>
<td>92</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>71</td>
</tr>
<tr>
<td>occipital lobe</td>
<td>40</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>35</td>
</tr>
<tr>
<td>cerebellum</td>
<td>29</td>
</tr>
<tr>
<td>other localizations</td>
<td>45</td>
</tr>
<tr>
<td>Karnofsky performance index, %</td>
<td>50—100</td>
</tr>
<tr>
<td>Status of the primary focus:</td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>249</td>
</tr>
<tr>
<td>progression</td>
<td>63</td>
</tr>
</tbody>
</table>

Table 2. Radiotherapy parameters for patients with from renal-cell cancer metastases to the brain (n=312)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Data range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV of the largest metastases, cm³</td>
<td>0,43—33,30</td>
<td>5,60</td>
</tr>
<tr>
<td>Prescribed isodose, %</td>
<td>20—92</td>
<td>50</td>
</tr>
<tr>
<td>Target marginal dose, Gy</td>
<td>10,0—27,6</td>
<td>20</td>
</tr>
</tbody>
</table>

Footnote: PTV — planning target volume.
MRI. The dynamics of MRI changes were classified as follows: complete response (elimination of metastasis), partial decrease in metastasis dimensions (decrease in tumor volume by 50% or more) (Fig. 1), lack of changes (<50%), increase in metastasis dimensions (>25%), and continued growth (tumor enlargement after its partial resection). FDG or methionine positron emission tomography (PET) (Fig. 2) or CT perfusion were used for differential diagnosis between tumor progression and possible formation of a post-radiation necrotic focus.

The neurological status was evaluated according to either presence or absence of one or several signs of neurological disorder (mental changes, speech disorders, diminution of strength or sense shock in limbs, hemiparesis, cerebral nerve dysfunction, paroxysmal symptoms, etc.). The evaluation was performed at the first GK STS, and subsequently once per 3–5 months.

Statistical analysis

Statistical analysis and processing of the material was performed using SPSS Statistics Version 20 software.

Lifetime of the patients (in months) was counted since GK STS. The analysis accounted for seven factors: patient’s age, Karnofsky performance status, condition of the primary tumor, number of metastases, presence of metastases in other organs, PTV of the largest metastases, and prescribed dose for the tumor of maximal volume. Survival rate after GK STS was a subject of actuarial analysis. Three methods of nonparametric and one method of parametric tests were used to determine potential risk factors influencing the lifetime. Nonparametric tests included: Log-rank, Breslow, and Tarone–Ware tests. The Cox proportional hazards model with stepwise variable selection (correlation between conditional probabilities) was used for parametric analysis. The parameters with significant \( p < 0.05 \) in at least one of the mentioned tests were considered as potential risk factors with respect to survivability.

Results

A program for coregistration of MR images in a Gamma Plan planning station was used to follow the dynamics of metastatic foci after radiotherapy.

Volumetric analysis

Dynamic volumetric measurements based on the MRI data based were performed in 188 patients out of 312 only because of MRI failure due to patient’s death, impairment in his/her condition, or data unavailability for another reason. Tumors of the largest volume only were considered in each patient. The following changes were detected according to the MRI results: complete treatment response in a metastasis – in 30 (16%) patients out of 188; partial decrease in metastasis volume – in 95 patients (51%), no changes in metastasis volume – in 44 patients (23%), increase in metastasis volume – in 19 patients (10%). Tumor progression was detected in 9 patients (5%); repeated GK STS was performed in seven of them, and symptomatic corticosteroid therapy was recommended for two others.
Fig. 2. Differential diagnostics between continued growth and post-radiation necrosis.

a – preoperative stereotactic MRI in T1 3D-VIBE mode with the contrast enhancement. The tumor (20x25x20.5 mm in size; volume of 5.3 cm³) surrounded with the perifocal locus can be seen in the right frontal area; b – the control contrast-enhanced MRI four months after the treatment. Tumor dimensions increased (the yellow line is the treatment isodose); c – PET with 11C-methionine four months after the radiotherapy procedure. An ametabolic region can be seen in the right frontal dose, corresponding to the PET signs of the tumor metabolic activity; d – the control contrast-enhanced MRI three years after the radiotherapy. No signs of continued tumor growth can be seen.

Table 3. Dynamics of the MRI changes after GK STS in the patients with renal-cell cancer metastases to the brain (n=188)

<table>
<thead>
<tr>
<th>Parameters of MRI changes</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>30</td>
</tr>
<tr>
<td>Partial decrease in metastasis volume (&gt;50%)</td>
<td>95</td>
</tr>
<tr>
<td>Lack of changes (&lt;50%)</td>
<td>44</td>
</tr>
<tr>
<td>Increase in metastasis volume (&gt;25%)</td>
<td>19</td>
</tr>
<tr>
<td>Continued growth</td>
<td>9</td>
</tr>
<tr>
<td>Emergence of new metastases</td>
<td>100</td>
</tr>
<tr>
<td>Abs. %</td>
<td>16</td>
</tr>
<tr>
<td>%</td>
<td>51</td>
</tr>
<tr>
<td>%</td>
<td>23</td>
</tr>
<tr>
<td>%</td>
<td>10</td>
</tr>
<tr>
<td>%</td>
<td>5</td>
</tr>
<tr>
<td>%</td>
<td>53</td>
</tr>
</tbody>
</table>
Repeated sessions of GK STS were performed in 73 patients (39%) for new brain metastases (Table 3).

**Neurological status**

The neurological status after GK STS was monitored in 210 patients out of 312. Before the first GK STS session, neurological impairment was detected in 158 patients (75%), while no neurologic symptoms were detected in 52 patients (25%). After GK STS, neurological impairment regressed in 46 patients (29%), while in 92 patients (58%), the neurological status remained unchanged. Before GK STS, aggravation of neurological deficit was detected in 20 patients (13%), including 12 cases with the deficit along with newly detected brain metastases, 2 – along with increased volume of a treated metastasis, and 6 – due to postradiation brain edema. In six patients (12%) out 52, who had no neurological impairment before GK STS, it occurred due to development of new brain metastases, while no neurological signs were detected in other 46 patients (84%). Thus, the aggravation (manifesting as neurological impairment) following GK STS took place in 26 cases (12%) out of 210; only eight of them (4%) were associated with GK STS (increase in a treated focus or postradiation edema).

**Survival rate and prognostic factors**

The median survival of 312 patients was eight months (Fig. 3). The median survival of the patients who died within the first year after GK STS was 6.03 months (1–12 months), while it was 27.9 months (13–91 months) in patients who survived longer than a year. The percentage of patients who survived more than 1 year after GK STS was 26%.

No effect of such parameters as patient’s age, volume, and number of metastases on the survival rate could be detected (the differences were not significant, \( p > 0.05 \)) (Fig. 4a–c). Favorable prognostic factors \( (p < 0.05) \) were as follows: Karnofsky performance index 70 or higher, controlled primary tumor and absence of extracranial metastases (Fig. 4d–f), as well as marginal dose per the largest metastasis more than 20 Gy (Fig. 4g, Table 4).

**Discussion**

Treatment of brain metastases includes such methods as radiotherapy, surgical removal of a tumor, STS, and their combination. Before the era of stereotactic me-

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Table 4. Medians of post GK STS lifetime in reference to various parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter value</th>
<th>Median lifetime, months</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;60 years</td>
<td>8</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>≥60 years</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Karnofsky scale index</td>
<td>≥70</td>
<td>8</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>&lt;70</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Primary focus control</td>
<td>under control</td>
<td>10</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>lack of control</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Metastases in other organs</td>
<td>not revealed</td>
<td>11</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>revealed</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Number of intracranial metastases</td>
<td>single metastases</td>
<td>8</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Volume of maximal metastasis</td>
<td>&lt;5 cm³</td>
<td>7</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>[5, 10], cm³</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm³</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Prescribed dose for the largest focus</td>
<td>&lt;20 Gy</td>
<td>7</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>≥20 Gy</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>
methods, whole brain radiation therapy was the main technique for treating brain metastatic lesions. However, this technique is inefficient [4, 7, 15, 38], especially in case of renal-cell cancer resistant to the conventional radiotherapy (e.g., [8]).

Surgical resection is the method of choice to control metastases over 3 cm in size [3, 10, 17, 28, 37]. Neurosurgical intervention is reasonable for patients with a single brain metastasis and favorable prognostic factors (i.e., controlled primary focus, no metastatic lesions in the internals, Karnofsky performance index of 70 or higher, and in cases when the large dimensions of a metastasis make STS impossible). Signs of intracranial hypertension and progressive focal symptoms are indica-
tions for tumor removal, which can rapidly improve patient’s condition.

GK STS is the current “golden standard” of radiosurgery; its high efficiency in treating brain metastatic lesions has been proved. The gist of this method is the use of stereotactic techniques for highly precise irradiation of small intracranial targets with narrow beams of ionizing radiation from the external sources [1, 4, 6, 13, 19].

The literature data, along with our own experience, prove the efficiency of treating patients with renal-cell cancer metastases to the brain using Gamma Knife radiosurgery. According to various authors [6, 13, 15, 19, 25, 29, 31, 35, 36], the median survival in patients with renal-cell cancer metastases to the brain is 7–15 months, with local control in more than 75% of patients.

In clinical practice, therapeutic decisions for patients with brain metastases depend on the stage of the neoplastic process and prognostic factors that influence the survival rate of patients. The key factors include patient’s condition, progression of extracranial tumors,
and the number of brain metastases. According to a number of authors [2, 7, 13, 20, 25, 31, 33], a group of patients with the Karnofsky performance index of 70 or higher, controlled primary focus, without metastases to other internals, without pronounced neurological impairment, and with the interval between the primary oncological diagnosis and detection of the brain metastases over 18 months is the most prognostically favorable group.

It should be mentioned that introduction of STS into clinical practice changes the general approach to treatment of renal-cell cancer: presence of brain metastases is not considered to be a factor determining the hopelessness of further treatment. Brain metastases can be adequately controlled with STS; however, a vast majority of patients die from progression of extracranial metastases and/or primary focus. The more positive prognosis requires wider application of various available means that allow a specialist to control primary tumor and metastases of various localizations. The successful experience in radiosurgery of brain metastatic lesions allows the authors to recommend using modern linear accelerators and cyclotrons equipped with appropriate navigation techniques for stereotactic irradiation in radiosurgery or hypofractionated irradiation modes and when a metastasis has extracranial location.

Conclusions

The study shows that highly efficient local control over the growth of renal-cell cancer metastases to the brain can be achieved using GK STS. A decrease in tumor dimensions or their stabilization was detected in 90% of patients, while tumor progression occurred in 5% of patients. In 88% of patients, STS was not followed by progression of neurological disorder. In 29% of patients, the neurological deficit regressed after GK STS. Deterioration associated with occurrence of neurological deficit or its aggravation was detected in 12% of patients. Only 4% of the aggravation cases could be caused by enlargement of an irradiated tumor or post-irradiation edema, while the others were caused by new metastases. Favorable prognostic factors included the Karnofsky performance index equal to 70 or higher, controlled primary tumor, absence of extracranial metastases, and marginal dose per the largest metastasis exceeding 20 Gy.

REFERENCES

The frequency rate of brain metastatic lesions in renal cancer patients is about 2–11%; its continuous growth is one of the important causes of treatment failures. The role of systemic drug therapy in treatment of patients with the progressing tumor process is steadily increasing. Current drug therapy of disseminated renal cancer includes cytokines (interleukin-2 and interferon-alfa), tirosin kinase inhibitors of VEGF receptor (sorafenib, sunitinib, pazopanib, and axitinib), anti-VEGF antibodies (bevacizumab), and mTOR inhibitors (temsirolimus and everolimus). Most antitumor drugs are characterized by poor penetrability through the hematoencephalic barrier due to low lipophilicity and/or high molecular weight. Surgery and radiotherapy, including radiosurgery, can be regarded as the optimal treatment methods for renal cancer patients with brain metastases. This study analyses 312 patients who underwent stereotactic Gamma Knife radiosurgery for renal cancer metastases to the brain. The authors provided a detailed protocol of irradiation for this challenging patient group and the standards for following up patients' dynamics. Progression was detected in 10% of cases only, while the neurological symptoms either regressed or remained unchanged in 87% of the patients. The median survival, 8 months, is noteworthy high. Unfortunately, the article presents no data on systemic drug therapy and on distribution of patients into RPA classes, which could contribute to its beauty. It should be mentioned, in conclusion, that stereotactic radiosurgery provides new possibilities for treatment of radioreistant brain metastases.

A.Kh. Bekyashev (Moscow)
According to foreign studies [1, 10, 11, 14-16], magnetic source imaging (MSI) provides reliable information on the localization of epileptic activity in the brain of a patient and thus it is one of the most efficient methods of presurgical noninvasive diagnostics. MSI is significantly superior to video electroencephalography monitoring (vEEG) in terms of its sensitivity to the sources of epileptic activity generated in spatially confined cortical neuronal ensembles and has higher accuracy in localizing these sources. The data obtained by interictal and ictal MSI, video EEG monitoring, electrocorticography, and postoperative outcomes in 13 patients demonstrated that location of the seizure-onset zone(s) according to the MSI data coincided with the ECoG data with accuracy to within a lobe. Due to its high sensitivity and specificity, MSI is a valuable tool for preoperative diagnosis of patients with medically intractable epilepsy. Magnetic source imaging can provide critical localization information that is not available in difficult-to-diagnose cases, such as the lack of epileptogenic injury zones according to the MRI data; ambiguous vEEG data; or discrepancy between the MRI, video EEG, and seizure semiology data.

**Keywords:** epilepsy surgery, magnetoencephalography, video EEG monitoring

According to foreign studies [1, 10, 11, 14-16], magnetic source imaging (MSI) provides reliable information on the localization of epileptic activity in the brain of a patient and thus it is one of the most efficient methods of presurgical noninvasive diagnostics. MSI is significantly superior to video electroencephalography monitoring (vEEG) in terms of its sensitivity to epileptic activity.

The present paper summarizes the first experience of application of MSI in our country. The objective of this study was to compare the results of noninvasive localization of epileptic activity foci obtained using vEEG and MSI methods in 22 patients with drug-resistant epilepsy who sought medical advice at the N.N. Burdenko Neurosurgical Institute and Russian Pediatric Clinical Hospital in 2010–2012. The sensitivities of the vEEG and MSI methods were compared; the comparison was based on the probability of detecting epileptic activity. The ratio between the number of epileptic activity foci detected according to vEEG or MSI and the total number of foci detected by both methods in 22 patients was considered as “working” definition of sensitivity. The percentage of foci localized identically by vEEG and MSI methods was evaluated, as well as the percentage of "mismatched" foci, i.e. those detected by only one method. At the next step the reliability of localization of epileptic foci by each method was verified in 13 patients who underwent invasive study using subdural electrodes followed by surgical resection. The success of surgical treatment was assessed by the outcomes according to the Engel scale [2].

**Methods**

**Characteristics of the population.** The study included 22 patients (aged 4 to 28 years, mean age 14.95±7.21 years) with drug-resistant epilepsy, who were candidates for surgical treatment. Drug-resistance was determined according to the criteria adopted by the International League Against Epilepsy (ILAE) [8]. All patients underwent preoperative examination using vEEG, MSI, and structural magnetic resonance imaging (MRI) methods. According to noninvasive tests (seizure semiology, vEEG, MRI), the seizure onset zone was presumably located in the temporal lobe in 7 patients; outside of the temporal lobe, in 15 patients. There were no pathological changes that cause epilepsy on MR images of 8 patients.

In most cases, vEEG and MRI results did not enable a definitive decision on surgical treatment. Additionally, MSI data were used in all cases. Single photon emission computed tomography was used in 3 patients as well.

Thirteen patients were operated. In 3 patients resective surgery was performed based on the results of noninvasive diagnostics, including MSI data. In 10 patients additional invasive studies were performed: intraoperative electrocorticography (ECoG) in 2 patients and chronic invasive EEG monitoring (duration 1–7 days).
in 8 patients. The data of all noninvasive diagnostic methods were used for navigation when installing subdural electrodes.

The success of surgical treatment was evaluated according to the Engel scale [2]. The follow-up period after surgery ranged from 7 to 35 months (average 21.46±9.75 months). Class I outcomes (A and B) were observed in 8 patients; class II (A and B) — in 3 patients, class IIIA — in 1 patient. In one case, surgical treatment did not alter patient’s condition (class IVB outcome).

Registration and analysis of vEEG and MSI data.

Interictal and ictal EEG was recorded in all patients in the state of wakefulness and sleep; study duration ranged from 1.5 to 72 h (average 31.12±26.94 h). Electrodes were positioned according to the "10–20%" international system (20 patients) and "10–10%" system (2). The EEG data were analyzed according to the standard criteria for evaluating the presence and topography of epileptic activity [13].

Intercital magnetoencephalography (MEG) was registered using a 306-channel Vectorview system (Elekta Neuromag, Finland), including 204 planar gradiometers and 102 magnetometers. The Neuromag software package (Finland) was used for data analysis. MEG study was conducted on the average for 2 h (40 min to 4.5 h) in patients in the state of sleep and after day-long sleep deprivation. Epileptiform patterns were distinguished according to the standard criteria used in EEG [13]. The equivalent current dipole model and the spherical head model [4] were used for localization of epileptic activity foci. The multipole modeling methods implemented in the Neuromag software package were applied when necessary [4]. Coordinates of reconstructed sources of epileptic events were combined with MRI of patients, thereby visualizing the location of neuronal sources of epileptiform events in the patient’s brain (MSI). A combination of at least 6 sources with a distance between the neighboring sources of at least 1 cm was considered as a cluster [12] and interpreted as irritative zone; i.e., the area of cortex which generates interictal epileptiform activity [9].

Comparison of the MSI and EEG data on localization of epileptic foci/irritative zones was conducted for interictal activity. The analysis comprised two stages. Stage I, 10 large regions in each hemisphere of the brain (Table 1) were determined based on respective location of EEG electrodes and Brodmann’s cytoarchitectonic areas [5, 6]. For each patient, clusters of epileptic activity sources (MSI) and EEG electrodes that registered local seizure activity were assigned to one of 10 defined regions of the cerebral cortex. In this case, the correspondence table of standard EEG electrode positions in the "10–10%" system and anatomical reference points of the cerebral cortex regions from the study by V. Jurcak et al. [6, 7] was used for EEG electrodes. Comparison of the location of the cluster sources in the patient’s brain and the map of Brodmann’s cytoarchitectonic areas of the cerebral cortex was used for MSI. It should be emphasized that MSI allows us to localize the area of irritation with accuracy up to 5 mm [5], whereas the spatial resolution of vEEG is significantly lower. At the step I of comparing, the MSI data on the spatial localization of clusters of sources were artificially roughened to equalize the conditions for vEEG and MSI in determining their sensitivity to the sources of epileptic activity;

<table>
<thead>
<tr>
<th>Region</th>
<th>EEG electrodes in the 10–20% system</th>
<th>Brodmann areas</th>
<th>Anatomical boundaries of the regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior frontal (Fant)</td>
<td>Fp1, Fp2</td>
<td>10, 11, 9, 46</td>
<td>From the pole of frontal lobe to precentral sulcus</td>
</tr>
<tr>
<td></td>
<td>Fz</td>
<td>6, 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F7, F8</td>
<td>45, 44, 47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F3, F4</td>
<td>8, 6, 9</td>
<td></td>
</tr>
<tr>
<td>Posterior frontal (Fpost)</td>
<td>F3, F4, C3, C4, Cz</td>
<td>4, 6</td>
<td>From precentral sulcus to central sulcus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>From the precentral sulcus to central sulcus</td>
</tr>
<tr>
<td>Frontoparietal (FP)</td>
<td>C3, C4, Cz, P3, P4, Pz</td>
<td>4, 1, 2, 3</td>
<td>At the junction of frontal and parietal lobes</td>
</tr>
<tr>
<td>Temporal (T)</td>
<td>T3, T4</td>
<td>21, 20, 38</td>
<td>Temporal lobe</td>
</tr>
<tr>
<td></td>
<td>T5, T5</td>
<td>37, 21, 22</td>
<td></td>
</tr>
<tr>
<td>Temporo-occipital (TO)</td>
<td>T5—O1, T6—O2</td>
<td>37, 19</td>
<td>At the junction of the temporal and occipital lobes</td>
</tr>
<tr>
<td>Temporo-parieto-occipital (TPO)</td>
<td>T5—P3, T6—P4</td>
<td>39, 40, 22, 19</td>
<td>At the junction of the temporal, parietal and occipital lobes</td>
</tr>
<tr>
<td>Temporo-parietal (TP)</td>
<td>T3—C3, T4—C4</td>
<td>40, 22</td>
<td>Posterior perisylvian area</td>
</tr>
<tr>
<td>Frontotemporal (FT)</td>
<td>T3—F7, T4—F8</td>
<td>47, 38, 44, 45, 11, 22</td>
<td>Anterior perisylvian area</td>
</tr>
<tr>
<td>Parietal (P)</td>
<td>P3, P4</td>
<td>19, 7</td>
<td>Parietal lobe</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Occipital (O)</td>
<td>O1, O2</td>
<td>19, 18</td>
<td>Occipital lobe</td>
</tr>
<tr>
<td></td>
<td>Oz</td>
<td>18, 17</td>
<td></td>
</tr>
</tbody>
</table>
location of irritative zones was evaluated in terms of the 10 selected regions in each hemisphere.

The ratio between the number of irritation foci detected by vEEG (vEEG+) or MSI (MSI+) and the total number of foci detected by both methods (vEEG+ and MSI+) in 22 patients was considered as “working” definition of sensitivity. The percentage of irritative zones localized identically by vEEG and MSI methods [(vEEG+ and MSI+) / (vEEG+ + MSI+)] and the percentage of “mismatched” areas detected by only one method [(vEEG+ and MSI-) / (vEEG+ + MSI-)] were determined (Fig. 1). In addition, taking advantage of MSI in spatial resolution, the location and the number of irritative zones were refined using the MSI data with accuracy up to lobar aspect — lateral, basal, medial, and opercular ones.

At step II of data analysis, the reliability of localization of the irritative zones was assessed based on vEEG and MSI data by comparing the data obtained for each method with the results of invasive examinations and/or postoperative outcomes in 13 patients who underwent surgical treatment.

Results

Sensitivity of MSI and vEEG methods. 75 irritative zones have been identified in 22 patients with drug-resistant forms of epilepsy using vEEG and MSI methods. About half (44%) of the irritative zones were detected by both methods (vEEG+ and MSI+), whereas the “mismatched” irritative zones were distributed as follows: 29 (39%) zones were identified only by MSI (vEEG- and MSI+) and 13 (17%) zones, only by vEEG (vEEG+ and MSI-) (Fig. 2a). The sensitivity to detection of irritation zones was 22% higher for the MSI method (Fig. 1).

In general, application of MSI enabled detecting irritative zones that had not been previously identified in 19 patients. More than half of irritative zones (17 of 29) that had not been identified by vEEG (vEEG+ and MSI+) were located in the frontal lobe. Nine of them were located on the medial, basal or opercular aspects of the frontal lobe (Fig. 2b).

In addition to increasing the number of detected irritative zones, application of MSI in 14 patients allowed one to obtain more precise information on the number and location of irritative zones that were detected by both methods with an accuracy of up to 10 large regions of the cerebral cortex (vEEG+ and MSI+). MSI data enabled separation of irritative zones closely spaced to each other, lying within the same region, as well as determining the lobar aspect with one or more irritative zones.

Thus, MSI has higher sensitivity to epileptic activity generated in spatially restricted neuronal ensemble of cortex as compared to vEEG. This superiority is particularly noticeable in those cases where irritative zones are located on the basal and medial cortical aspect, i.e. in the areas located far from the EEG pickup electrode. This fact can be caused by several factors, the most important ones are the independence of the magnetic component of the source field of tissues conductivity, the absence of “averaging” properties of cranial bones for this component and the absence of “spreading” of currents in the intermeningeal space of the brain during propagation of the electromagnetic signal from the excited tissue [4].

Verification of the MSI and vEEG data on localization of irritative zones. The final results of application of all the methods of preoperative and intraoperative diagnostics and the outcomes of subsequent surgical treatment in 13 patients (Table 2) were compared. Reliability and accuracy of localization of irritative zones by vEEG and MSI were evaluated by comparing with ECoG. Twenty-one irritative zones were covered with electrodes and confirmed in 10 patients. However, only 9 of them were found by both methods (vEEG+ and MSI+), whereas 12 zones were found only by MSI (vEEG+ and MSI+). Additional zones found by MSI are predominantly localized on the basal and medial aspects of the brain lobes (Fig. 3). In the same 10 patients, 3 irritative zones were found only by EEG (vEEG+ and MSI+). However, they were not covered with electrodes during ECoG, since their clinical significance was unclear.

In order to assess the clinical significance of 12 irritative zones identified only by MSI (vEEG+ and MSI+), all irritative zones detected by vEEG and MSI were compared with seizure onset zones according to the ECoG data. As a result of this comparison, 5 variants of combinations of MSI and vEEG data and seizure onset zones were distinguished (Fig. 4):

1. vEEG and MSI data completely coincided with the location of seizure onset zones according to ECoG (1 patient).
II. **vEEG** data assumed the vast seizure onset zone. According to MSI data, two closely spaced irritative zones have been identified at the same boundaries; however, only one of them was the seizure onset zone. The conclusion drawn from the MSI data was confirmed by the ECoG data (2 patients).

III. Both MSI and **vEEG** data pointed to the same seizure onset zones, but according to MSI data zone boundaries were expanded as additional sources localized on the other aspect of the same lobe were detected. MSI results led to changes in program of invasive diagnostics and areas at both aspects of the corresponding lobe were covered with pick-up electrodes during ECoG. ECoG confirmed the conclusion made according to MSI (5 patients). The case of patient B.L. (**Table 2**) is provided to illustrate this variant (**Fig. 5**).

IV. There was a discrepancy between the MSI and **vEEG** data on seizure onset zone. The MSI data have shown that the true seizure onset zones were not detected by **vEEG** and located away from the zone of propagation of epileptic activity, which was misidentified by **vEEG** as a seizure onset zone. The MSI data have radically changed the positioning of electrodes during ECoG. The MSI data were confirmed by ECoG (1 patient).

V. In a patient with tuberous sclerosis and multiple structural brain lesions, the locations of all irritative zones have been identified using the **vEEG** data, but the seizure onset zone has not been determined. The seizure onset zone was revealed using the MSI data. ECoG confirmed the conclusion made according to the MSI data (1 patient).

**Case report.** A 28-year-old female patient with refractory epilepsy suffering from dialeptic, asymmetrical tonic seizures with secondary generalization and preceding autonomic aura. No structural brain abnormalities were found according to the MRI data. Interictal EEG included electrographic seizures (long sequence of epi-

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**Fig. 2.** Ratio between (a) the number of irritative zones identified using MSI (blue), **vEEG** (lilac) or both methods (Brown), and (b) the number of **vEEG** and MSI irritative zones localized on different lobar aspects. Distribution over 10 regions of the neocortex

Numbers above the columns of the histogram show the total number of irritative zones for each region. Regions Fant and Fpost are combined to the region F. Regions FT, TP, TPO have only the lateral aspects. No irritative zones have been identified at TO regions; no irritative zones classified as **vEEG** and MSI have been identified in the FP region.

**Fig. 3.** Ratio between the number of irritative zones localized on different lobar aspects of the brain and confirmed by the ECoG data; distribution over 10 regions of the neocortex.

Zone identified by both methods (MSI and **vEEG**) are hatched; zones identified only by MSI (**vEEG** and MSI) are not hatched. The numbers above the columns of the histogram show the total number of irritative zones for each region. Regions Fant and Fpost are combined to the region F. Region FT has only lateral aspect.
The same region has been identified as seizure onset zone based on ictal activity in EEG. Interictal MSI analysis allowed identifying two independent clusters of electrographic seizure sources. Both clusters were located in the temporo-occipital region; one of them was located on the lateral aspect and the other, on the basal aspect of the occipital lobe. Based on the MSI data, the strategy of subdural electrodes positioning during invasive monitoring was changed. A grid with 64 electrodes was placed on the lateral aspect of the temporo-occipital brain region. Additional grids with 20 and 8 electrodes were placed on the medial and basal aspects of the right occipital lobe. Three typical epileptic attacks were registered during 3 days. The seizure onset zone was located under 3 electrodes of the 64-contact grid with instant propagation recorded by nine other electrodes of the same grid and two electrodes of the 8-contact grid. No epileptic activity was registered under the electrodes of 20-contact grid. Based on the results of invasive monitoring, tailored resection was performed during surgery: parts of the cortex on the basal and lateral aspects of the occipital lobe were removed, corresponding to the location of the electrodes that recorded ictal activity. Duration of the postoperative period was 1.5 years. The outcome of surgical treatment according to the Engel scale was 1B.

Table 2. Results of noninvasive and invasive diagnostic methods, resection areas and post-surgical outcomes in 13 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Assumed side</th>
<th>MRI</th>
<th>vEEG, semiotics</th>
<th>MSI</th>
<th>ECoG (seizure onset)</th>
<th>Type and region of resection</th>
<th>Biopsy</th>
<th>Outcome by Engel</th>
<th>Postoperative period, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.L.</td>
<td>24</td>
<td>R</td>
<td>FCD</td>
<td>TL</td>
<td>TL b, m, m, FL1</td>
<td>TL b, m, GFI, GFM</td>
<td>Anteromedial temporal lobectomy on the right, tailored frontal lobe resection on the right</td>
<td>FCD, type 1B</td>
<td>IA</td>
<td>35</td>
</tr>
<tr>
<td>S.I.</td>
<td>28</td>
<td>R</td>
<td>HS, FCD TL</td>
<td>FT</td>
<td>TL l, b</td>
<td>TL</td>
<td>Anteromedial temporal lobectomy on the right</td>
<td>HS, FCD type 1B</td>
<td>IA</td>
<td>35</td>
</tr>
<tr>
<td>K.P.</td>
<td>10</td>
<td>L</td>
<td>HS, FCD TL</td>
<td>TL</td>
<td>—</td>
<td>Anteromedial temporal lobectomy on the left</td>
<td>HS</td>
<td>IB</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>S.A.</td>
<td>5</td>
<td>R+L</td>
<td>TC</td>
<td>R FL, L OL, L TL</td>
<td>R FL</td>
<td>—</td>
<td>Selective removal of lesion in the frontal lobe</td>
<td>TC</td>
<td>IB</td>
<td>29</td>
</tr>
<tr>
<td>S.A.</td>
<td>19</td>
<td>R</td>
<td>FCD</td>
<td>TL</td>
<td>TL b, m, m, R FL, R FL</td>
<td>Selective removal of lesion in the frontal lobe</td>
<td>FCD types 1IA and 1IB</td>
<td>IA</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>M.V.</td>
<td>18</td>
<td>R</td>
<td>n/a</td>
<td>FP</td>
<td>GFI</td>
<td>GFI, GFM</td>
<td>Tailored frontal lobe resection on the right</td>
<td>FCD types 1A and 1C porencephalic cystic, FCD</td>
<td>IA</td>
<td>12</td>
</tr>
<tr>
<td>M.D.</td>
<td>8</td>
<td>R</td>
<td>Cystic glial changes</td>
<td>TPO</td>
<td>OL b, 1</td>
<td>Tailored occipital lobe resection on the right</td>
<td>GFI, GFM</td>
<td>IIA</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>S.A.</td>
<td>19</td>
<td>R</td>
<td>n/a</td>
<td>FL</td>
<td>FL b, o, 1</td>
<td>1) GFS, 2) GFI, GOA, GOL</td>
<td>Tailored frontal lobe resection on the right</td>
<td>FCD type 1IA</td>
<td>IVB</td>
<td>18</td>
</tr>
<tr>
<td>L.I.</td>
<td>20</td>
<td>L</td>
<td>HS</td>
<td>FT</td>
<td>TL b, m</td>
<td>TL m</td>
<td>Anteromedial temporal lobectomy on the left</td>
<td>FCD type 1C</td>
<td>IIA</td>
<td>12</td>
</tr>
<tr>
<td>S.M.</td>
<td>7</td>
<td>L</td>
<td>p/o FP</td>
<td>FP</td>
<td>FL o, 1</td>
<td>—</td>
<td>Frontal lobectomy on the left</td>
<td>—</td>
<td>IIA</td>
<td>17</td>
</tr>
<tr>
<td>B.L.</td>
<td>28</td>
<td>R</td>
<td>n/a</td>
<td>TO</td>
<td>TO b, 1</td>
<td>OL b, 1</td>
<td>Tailored occipital lobe resection on the right</td>
<td>FCD type 1IA</td>
<td>IB</td>
<td>18</td>
</tr>
<tr>
<td>O.A.</td>
<td>18</td>
<td>R</td>
<td>cystic PL</td>
<td>PL</td>
<td>PL</td>
<td>—</td>
<td>Selective removal of lesion in the parietal lobe on the right</td>
<td>FCD type 1C porencephalic astrocytic glioma</td>
<td>IA</td>
<td>11</td>
</tr>
<tr>
<td>K.A.</td>
<td>14</td>
<td>—</td>
<td>n/a</td>
<td>Vertex</td>
<td>L poste- rior FL</td>
<td>L FP l</td>
<td>Tailored frontoparietal lobe resection on the left</td>
<td>FCD type 1C</td>
<td>IIIA</td>
<td>7</td>
</tr>
</tbody>
</table>

**Conclusion**

Analysis of the results of comparing the MSI, vEEG and ECoG data in patients with drug-resistant epilepsy has shown that high sensitivity and specificity of MSI during detection and localization of epileptic activity sources in the human brain makes it a valuable tool for preoperative examination stage in patients with drug-resistant epilepsy. Application of MSI during the preoperative examination stage is most valuable in difficult...
diagnostic cases, such as the absence of the epileptogenic zones on MRI, ambiguity of the vEEG data or discrepancy between the vEEG, MRI and data on semiotics of attacks. Application of MSI in addition to the standard noninvasive diagnostic methods (vEEG, MSI) significantly affects further planning of invasive studies and choice of strategy and tactics of surgical treatment.

REFERENCES

The Role of Neurotransmitters and Cytokines in the Pathogenesis of Acute Traumatic Brain Injury

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The aim of the study was to investigate serum serotonin levels and to compare the results with inflammatory markers in patients with acute traumatic brain injury. We examined the cytokine, serotonin, and psychovisual status in 72 patients with traumatic brain injury of mild to moderate severity. Depending on injury severity, the increase in serotonin level was found to correlate with the anti-inflammatory cytokine markers. Measuring serum serotonin levels can serve as a method for differential diagnosis of cerebral concussion and contusion.

Keywords: brain injury, serotonin, cytokines.

Brain injury results in a combination of pathophysiological reactions, including primary and secondary damage to brain tissues, such as inflammation, hypoxia, necrosis, apoptosis, disorders of synaptic plasticity and functional neuronal activity. In patients with traumatic brain injury (TBI), the destruction and repair processes develop simultaneously in the central nervous system (CNS), mainly in neurons and glia [1, 2]. Inflammatory response is caused by the primary structural changes in the brain and results in massive release of cytokines (pro-inflammatory and anti-inflammatory), nitrous oxide, proteases, eicosanoids, lysozyme, etc. [3]. Cytokines are synthesized by activated macro- and microglia, damaged vascular endothelium, and immune system cells mobilized to the injury site and the adjacent areas as a result of changes in the hematocerebral barrier permeability [3–5]. The cytokine effect is closely related to physiological and pathophysiological responses of the organism. Both local and systemic defense mechanisms become modulated. One of the most important cytokine functions is orchestrating the interplay between the immune, endocrine, and nervous systems in response to stress (i.e. TBI). An important link in brain response to an injury is a change in metabolism of neurotransmitters, including serotonin. Neurotransmitter mechanisms are involved both in formation and neutralization of traumatic brain injury [2, 6, 7]. Neurotransmitter metabolism disorder is the most important feature of the TBI pathogenesis. Serotonin is one of the main mediators of stress-limiting system [8]; it may be very important in clinical practice to measure alterations in its level. Serotonin exhibits a broad range of effects in the human organism since the early stages of embryonic development. Experimental data suggest on the negative effect of serotonin deficit for natal hypoxia retardates rooting of serotonergic fibers into the hippocampus and cortex; serotonergic axonal degeneration increases, resulting in biogenic amine imbalance in the fetal brain [10]. A.A. Tkachenko [11] has demonstrated that serum serotonin level is characterized by higher lability and responses rapidly to stress. F. Artigas [12] regarded serotonin content in peripheral blood plasma as a factor related to serotonin concentration in the extracellular space of the brain (including the synaptic space). Some data suggest that the serotonergic system is involved in immunogenesis control. The interplay between the immune and nervous systems has two directions [13]. Cytokine receptors are found in the CNS; on the other hand, neurotransmitter receptors were found in the lymphoid tissue. This ensures the interplay between the neuroendocrine and the immune systems. While the involvement of the immunocompetent system in the traumatic process is considered to be proved [14, 15], the role of serotonin in the pathogenesis still remains unclear.

The aim of the study was to investigate serum serotonin levels and to compare the results with inflammatory markers in patients with acute traumatic brain injury.

Materials and Methods

A total of 72 patients aged 18–62 years (the mean age 31.5±13.3 years) were included in the study (52 males and 20 females). The patients were divided into three groups depending on the severity of the closed head injury. Twenty-seven patients with cerebral concussion were included in the first group, 17 patients with mild cerebral contusion were included in the second group; the third group contained 28 patients with moderate cerebral contusion. Fifteen individuals with no history of TBI were in the control group. Gender and age were nearly equal between the groups.
All patients were examined one day after TBI (at admission to the Neuro-traumatologic Department) by general clinical, neurological, and instrumental methods: X-ray of the skull, echoencephalography, ophthalmoscopy, and CT of the brain. The neurological deficit was assessed using the Glasgow Coma Scale (GCS) and NIHSS, where each neurologic symptom is matched with a certain score. The Barthel Index of Activities of Daily Living was used to evaluate the independence of patients. All patients underwent a psychometric test using the Montgomery–Asberg Depression Rating Scale, the Hospital Depression and Anxiety Scale, and the Spielberger–Hanin inventory to assess the levels of reactive and personal anxiety. vegetative dystonia was ascertained using the questionnaire (subjective assessment of the condition) and the scheme (objective assessment of the vegetative disorder) proposed by the Republican Center for Vegetative Pathology (A.M. Vein et al.). Humoral serotonin content in peripheral blood serum was measured by solid-phase enzyme immunoassay using an IBL Serotonin ELISA kit. Serotonin content was expressed as ng/ml. Immunological assay of serum and cerebrospinal fluid (CSF) for tumor necrosis factor (TNF, one of the main pro-inflammatory cytokines) and interleukin-10 (anti-inflammatory cytokine) were used for unbiased estimation of pathological inflammatory processes. Solid-phase enzyme immunoassay with test kits (OOO “Tsitokin”, St. Petersburg) was used to measure the cytokine level according to the manufacturer’s instructions. Cytokine content was expressed as pg/ml. Blood and CSF samples were collected 1–2 days after the injury.

Statistical data processing was performed with the Statistica 6.0 software package using descriptive statistics: determining the sample mean (M) and the standard deviation (σ), non-parametric methods (comparison of independent groups using the Mann–Whitney test). Analysis of dependences was performed using the Spearman’s rank correlation coefficient (r). Differences were significant at the p<0.05.

Results

Patients’ complaints were typical of the acute period of TBI: headache (82%), fatigue (69%), dizziness (54%), and sleep disorders (35%) were the most frequent complaints. Clinical and neurological examinations detected focal neurologic and meningeal syndromes in most cases of cerebral contusion. Assessment of consciousness according to the GCS showed that difference between patients with cerebral contusion and concussion was not significant (score of 14.3±1.8 and 15.0±0.8, respectively). The mean NIHSS scale score was 2.55±1.88. Significance of differences in the neurological status between patients with concussion (0.88±0.8) and mild contusion (3.08±0.9) was p=0.0001; between patients with mild contusion and moderate contusion (4.3±1.3), p=0.009. The disability level according to the Barthel scale was significantly higher (p=0.032) in patients with mild contusion (97.5±6.2) than in those with concussion (100); in patients with moderate contusion, it was 88.46±15.02 (p=0.003 with respect to the concussion group and p=0.04 with respect to the mild concussion group).

A significant level of depression according to the Montgomery–Asberg Depression Rating Scale in the acute period of TBI was detected in patients with concussion (8.67±5.02 points), mild contusion (10.75±9.72), and moderate contusion (11.95±8.96) compared to the control group (score of 3.1±1.9 points; p=0.05 for all groups). The mean anxiety and depression levels according to the Hospital Scale were 5.37±3.18 and 3.78±3.03, respectively, in concussion patients, 4.83±4.36 and 4.83±3.27 in patients with mild contusion, and 6.18±4.02 and 5.68±4.12 in patients with moderate contusion. No significant differences in these values were detected.

The data obtained using the Spielberger–Hanin questionnaire showed moderate reactive and mild personal anxiety in most cases. The mean score of reactive anxiety was as follows: 44.7±9.78 in the concussion group; 45.18±14.12 in the mild contusion group; and 47.95±9.64 in the moderate contusion group; these values were significantly higher than those in the control group (32.5±3.2). The mean score of personal anxiety was as follows: 38.74±8.86 in the concussion group; 40.9±9.17 in the mild contusion group; and 40.95±10.41 in the moderate contusion group, which did not differ significantly from the control group (32.7±3.8). The vegetative dystonia score did not significantly differ from that in the control group. The score was assessed using the questionnaire and the scheme, respectively: 20.15±14.52 and 22.07±13.09 in the control group; 18.83±11.03 and 17.33±11.77 in the mild contusion group; and 15.82±14.21 and 19.45±15.21 in the moderate contusion group.

A significant difference in the interleukine-10 content in blood serum was found between patients with concussion (6.0±9.9 pg/ml) and moderate contusion (0.4±1.7 pg/ml; p=0.03). The TNF content in blood serum was significantly different (p=0.039) between the concussion group (5.03±8.72 pg/ml) and the moderate contusion group (34.14±24.5 pg/ml). The interleukine-10 content in CSF fluctuated between 0.0 and 6.3 pg/ml (2.37±1.2 pg/ml on average). The mean TNF content in CSF was 50.8±17.4 pg/ml. No significant differences depending on contusion severity were found in the CSF cytokine content. The linear correlation was found between the neurological status and the levels of interleukine-10 (r=−0.36; p=0.04) and TNF (r=−0.41; p<0.02) in blood serum. These data attest to the fact that there is an objective dependence between clinical symptoms and the severity of closed head injury.

Serotonin level in blood serum in concussion patients was 148.90±59.57 ng/ml, which does not differ (p>0.05) from the control group (187.2±28.9 ng/ml). The serum serotonin concentration in the mild contu-
The correlation analysis revealed dependence of serotonin concentration on the type of closed head injury ($r = 0.35$; $p = 0.02$). Serotonin level increases together with TBI severity. The humoral serotonin level in patients in the acute period of TBI was independent of the severity of psychoemotional and vegetative disorders. Serotonin content in the CSF reversely correlated ($r = -0.7$; $p = 0.05$) with the TNF level in CSF (Fig. 2);

![Fig. 1](image1.png)  
*Fig. 1. Diagram showing the range of serotonin level in blood serum in patients with TBI of different severity.*

![Fig. 2](image2.png)  
*Fig. 2. Correlation ($r = -0.7$; $p = 0.05$) between serotonin and TNF content in cerebrospinal fluid in patients with TBI.*
and anti-inflammatory cytokine contents were balanced and correlated with the severity of neurological symptoms, giving an independent estimate to the TBI severity. Serum serotonin level was directly proportional to CSF interleukin-10 content, while CSF serotonin content reversely correlated with the TNF level in CSF. Serum serotonin level could serve as a diagnostic marker of TBI severity and can be used the first day after TBI for differential diagnosis of concussion and mild contusion of the brain. Correlation analysis revealed that serotonin can be considered as a mediator involved in the anti-inflammatory mechanisms of brain protection in patients with mild or moderate contusion. Studying the serotonin neurotransmitter and cytokine profiles in the acute period of the closed head injury is of both theoretical and practical significance due to its potential in estimating the severity of a damage to the nervous tissue, in predicting results, inflammatory complications and activity of the reparative processes in the central nervous system.

serum serotonin level was proportional \( (r=0.7; p=0.05) \) to interleukin-10 content in CSF (Fig. 3). The neurological disorders in our study influenced the Barthel scale score \( (r=-0.51; p=0.002) \).

**Discussion**

Significant changes in neither psychoemotional nor vegetative status were found in patients in the acute period of closed head injury of different severity (concussion, mild or moderate contusion). Psychovegetative syndrome in the acute period of TBI could be regarded as a non-specific reaction to the traumatic and/or stress effect. Cytokine content in blood serum and CSF represents non-specific (universal, reactive) inflammatory processes that are typical of TBI depending on injury severity: the highest level of pro-inflammatory TNF was found in patients with moderate cerebral contusion. Significantly higher levels of anti-inflammatory interleukin-10 were found in patients with mild TBI. Pro-

Fig. 3. Correlation \( (r=0.7; p=0.05) \) between serum serotonin and interleukin-10 content in CSF in patients with TBI.

**REFERENCES**


All brain neurotransmitter mechanisms are currently known to be involved in the pathogenesis of traumatic brain injury. In particular, excessive amounts of neurotransmitters are released during the acute period of injury; glutamate release is most dangerous, since it induces excitotoxicity mechanisms. The experimental and clinical data obtained by many authors suggest that excessive amounts of acetylcholine, dopamine, and serotonin in the acute period of injury correlate with a more unfavorable prognosis. The effect of excessive amounts of monoaminergic neurotransmitters has been studied insufficiently. However, it was demonstrated on the experimental and clinical data obtained by many authors that increased serotonin level reduces glucose uptake, activates excitotoxicity processes, while treatment with common serotonin receptor agonists (except for selective 5HT1a agonists) does not provide better results. This fact suggests that serotonin excess plays a negative role in pathogenesis of traumatic brain disease. The excessive amount of neurotransmitters gradually decreases over the first weeks after injury; however, precise timing for injuries of different severity is unknown.

The serotonergic system, together with the noradrenergic, dopaminergic and cholinergic ones, are neuromodulatory systems that play crucial role in the adaptive behavior. In particular, the serotonergic system is activated in response to stress or danger. It is known from experiments that hyperactivation of dorsal raphe nucleus (the center of the serotonergic system in the medulla oblongata) under controlled stress can be blocked by the prefrontal cortex of the frontal lobes, which is not the case under uncontrolled stress. Thus, the dependence of serum serotonin level in the acute period on injury severity demonstrated in this study has a pathophysiological explanation and is of both practical and fundamental importance. Unfortunately, the authors have not provided a comprehensive comparison with foreign studies.

Investigation of poorly studied neuro-immune interactions is another merit of the authors. It is known that acute stress increases the levels of catecholamines and cortisol, as well as causes a release of serotonin from platelets, humoral immunity activation (ThII), increase in B-lymphocyte and natural killer cell count, an increase in levels of interleukins-4–6, 10. In the present study, the authors have obtained interesting results on the correlations between the serum serotonin content and anti-inflammatory interleukin-10 level in the CSF, between the CSF serotonin and TNF contents in patients with injuries of mild and moderate severity. These facts suggest that serotonin level can reflect severity and direction of the neuroinflammatory response to the injury.

Therefore, this study is rather up-to-date as it focuses on neuro-immune interactions in patients with traumatic brain injuries of different severity, which is rather topical and insufficiently studied.

E.V. Aleksandrova (Moscow)
Injury to the Cavernous Segment of the Internal Carotid Artery upon Transsphenoidal Endoscopic Removal of Pituitary Adenomas (Report of Four Cases).


N.N. Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences, Moscow, Russia

An endoscopic endonasal transsphenoidal approach for removal of pituitary adenomas and other tumors of the sellar region is an effective and relatively safe method in most cases [1–7, 13]. In recent years, the technique of endoscopic endonasal transsphenoidal removal of formations of the chiasmosellar area has been successfully implemented and actively used at the Burdenko Neurosurgical Institute (NSI). Currently, over 400 patients are operated on using this technique at the NSI annually.

One of the most serious complications of transsphenoidal surgery is injury to the cavernous segment of the internal carotid artery (ICA), which is observed, according to different authors, in 0 to 3.8% of cases. A total of 3,000 patients with pituitary adenomas had been operated on at the Institute of Neurosurgery using the standard endoscopic transsphenoidal approach in the period from 2005 to March 2013; of whom injury to the ICA occurred in 4 (0.13%) patients. All patients with injury to the ICA were examined with angiography, which revealed: 1 case of ICA occlusion and 3 cases of the false aneurysm formation. Three patients received endovascular treatment. ICA injury can be due to the incorrect orientation in the surgical wound or excessively aggressive manipulations in the cavernous sinus. The choice of an endovascular treatment method upon ICA injury depends on availability of adequate collateral circulation and ICA tortuosity. Injury to the cavernous segment of the ICA upon transsphenoidal surgery is a rare, but dangerous and potentially fatal complication. Upon the endoscopic transsphenoidal approach, removal of tumors of the chiasmosellar area, correct identification of the middle line as well as location of the ICA is important; the use of different navigation systems and Doppler ultrasound is possible for this purpose.

Keywords: endoscopic endonasal surgery, pituitary adenoma, ICA injury.
local spasm in a response to ICA injury, by thrombosis, or by tight packing of the cavernous sinus cavity with hemostatic materials.

Unlike true aneurysms, FAs occur due to rupture of all layers of the vessel wall with the formation of the aneurysm "wall" by surrounding structures. FAs may cause massive nasal bleedings, CCF formation, and subarachnoid hemorrhage. As a result of the possible clot formation in the injured vessel or FA, this group of patients has an increased risk of the ischemic stroke development of the brain due to thromboembolism [14, 17].

In the literature [15, 18], different techniques for treatment of ICA injuries using endovascular surgery have been described. When choosing a particular method for endovascular treatment, it is necessary to focus on the presence or absence of adequate collateral circulation as well as on anatomical features of the vessel [5]. For ICA occlusion directly at the FA level, a latex balloon catheter had been used previously. However, taking into account a possibility of vessel recanalization, due to the cylinder volume reduction, and a risk for an increase in an already existing lesion of the vessel wall upon blowing a balloon, this technique is not used at present.

Placement of stent grafts at the ICA rupture level is possible. However, stent grafts are rigid devices, which complicates their passage through tortuous vessels. Upon that stent grafts can be used on a confined portion of the vessel where there are no rami of significant arteries. Moreover, they have a high risk for thrombosis development [5].

Currently, the main method is endovascular trapping (exclusion of the ICA with FA from blood flow) using microcoils and an adhesive composition.

Cases from our practice are presented. Patients’ characteristics are given in the Table.

Case 1

A 54-year-old female patient. The tumor spread infrasellarly, destroyed the sella turcica floor. Under these conditions, bony landmarks, which could be used to localize the middle line, were not visible. Injury to the left ICA occurred due to incorrect identification of the middle line at the stage of tumor removal with tumor forceps. It should be noted that bleeding was stopped by tight packing of the cavernous sinus area with hemostatic materials. Left ICA occlusion was revealed by angiography (Fig. 1). In this situation, any additional occlusion or reconstructive surgery of the ICA was considered unadvisable. Further in this patient diffuse cerebral edema developed and increased intracranial pressure to 35–40 mm Hg was noted that were associated with vasospasm developed in the left anterior cerebral artery (ACA) and a reduction in blood flow in the left middle cerebral artery (MCA). This required bilateral decompressive trepanation, which was performed on the 7th day after the operation. During the surgery, hemorrhage to ischemic parts of the brain with the development of dislocation syndrome occurred (Fig. 2). The patient died on the 9th day after the surgery.

Case 2

A 61-year-old male patient. Injury to the cavernous segment of the right ICA occurred at the approach stage during resection of the DM of the sella turcica floor using microsurgical scissors. Preoperative MRI demonstrated the medial displacement of the cavernous segment

*Fig. 1. Case 1. Total selective angiography.*

a – the proximal portion of the left ICA 3 cm above the bifurcation of the left common carotid artery is contrasted; b – the right common, external, and internal carotid arteries are contrasted, the territory of the left MCA and ACA is well fed through the anterior carotid artery.
of the right ICA (Fig. 3). An angiographic examination revealed a defect in the ICA wall. It should be noted that the collateral blood supply from the opposite ICA was satisfactory (Fig. 4). Because of carotid artery tortuosity, which made it impossible to perform reconstructive surgery with preservation of blood flow through the ICA, occlusion of the right ICA at the defect level was performed (Fig. 5). According to the Doppler ultrasound data of brain vessels on the 1st day after the operation, blood flow in the anterior (ACA) and posterior communicating artery (PCA) remained, but was significantly reduced in the right MCA. On the 1st day after surgery, the circulatory failure and ischemia of the right hemisphere of the brain with the development of right hemispheric edema occurred, which eventually led to death due to dislocation syndrome on the 6th day after the operation (Fig. 6).

Case 3

A 40-year-old female patient. MRI of the brain revealed an intrasellar pituitary tumor (Fig. 7). Injury to the cavernous segment of the ICA occurred at the approach stage during trepanation of the sella turcica floor with forceps. In this patient, the anatomy of the posterior wall of the sphenoid sinus was grossly altered because of acromegaly. An angiographic study revealed a lesion of the anterior siphon of the left ICA below the ramus of the left ophthalmic artery (Fig. 8a), which required occlusion of the left ICA at the rupture level with preservation of the left ophthalmic artery (Fig. 9). It should be noted that the collateral blood supply from the opposite ICA was satisfactory (see Fig. 8b). The patient was discharged without the appearance/augmentation of focal neurological symptomatology.

Case 4

A 46-year-old male patient. Intra- and latero-(D,S)sellar prolactinoma (Fig. 10). Injury to the right ICA occurred at the hemostasis stage after tumor removal from the cavernous sinus cavity. Angiography, carried out immediately after surgery, did not reveal

Fig. 2. Case 1. Postoperative CT scans.

a – expansion of the ventricular system, compression of the basal cisterns, massive subarachnoid hemorrhage; b – foci of hemorrhage to the ischemia area along the convexal surface of the left hemisphere, a sharp increase in swelling of the left hemisphere with a large displacement of the middle line structures.

Fig. 3. Case 2. MRI of the brain before surgery.

Intra-, supra-, latero(D,S)sellar pituitary adenoma (arrow indicates the medial displacement of the cavernous segment of the right ICA) is revealed.
Fig. 4. Case 2. Angiography after the surgery (a). The study of collateral blood flow (b).

a – a lesion on the ventral wall of the anterior knee siphon of the right ICA (arrow) is revealed; b – the external and internal carotid arteries left are contrasted, the territory of the right MCA and ACA is well fed through the anterior carotid artery.

Fig. 5. Case 2. Balloon occlusion of the right ICA at the wall lesion level (black arrow); the second balloon is additionally placed at the level of the petrous segment of the ICA (red arrow).

Fig. 6. Case 2. MRI of the brain.

The 1st day after operation (a: extended focal and diffuse ischemic changes in the white and gray matter of the right hemisphere are visualized with an arrow); CT scan of the brain. The 3rd day after the operation (b).

Fig. 7. Case 3. MRI of the brain.

The intrasellar pituitary tumor is revealed.
obvious signs of injury to the internal and external carotid arteries indicating the source of bleeding. The FA formation was detected upon repeated angiography on the 8th day after the operation (Fig. 11). According to the angiography data, hypoplastic right A1 and P1 were revealed. Under these conditions, it was impossible to conduct occlusion of the ICA. A stent graft was placed to the patient on the 9th day after the operation (Fig. 12). The patient was discharged without augmentation of focal neurological symptomatology.

**Discussion**

A total of 3,000 patients with pituitary adenomas had been operated on at the NSI using the endoscopic trans-
could not be stopped under the control of an endoscope. To eliminate bleeding, various hemostatic materials were used (Table). After bleeding had been stopped, all patients, under conditions of a specialized X-ray operation room, were subject to angiography (from this step, treatment modality for patients was determined in cooperation with endovascular surgeons) (Table).

According to J. Raymond and J. Hardy [8], there are factors increasing risk of ICA injury during transsphenoidal surgery: tumor invasion into the cavernous sinus, previous transsphenoidal operations or radiation therapy as well as acromegaly.

The analysis of preoperative neurovisualization data is an important component in the operation plan-

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**Fig. 11. Case 4. Total angiography on the 8th day after the operation.**

a — the wall lesion of the cavernous segment of the right ICA located in the anterior knee siphon area; b — a 3D reconstruction (FA is indicated by the arrow); c, d — angiography under clipping of the right common carotid artery in the neck demonstrated the hypoplastic ACA and PCA.
MRI and CT data allow one to study the relationship between the anatomical structures of the chiasmosellar area, to determine the size of the sphenoid sinus and degree of its pneumatization. When approaching the sella turcica floor, it is necessary to always follow the middle line. The middle line is primarily determined by the nasal septum. Other reference points are: the ramp located along the middle line below the sella turcica floor; bony prominences of the anterior knee of the ICA located laterally to the sella turcica floor; the opticocarotid recess; the rostrum (whose remains may stay after trepanation of the anterior wall of the sphenoid sinus).

Upon this, an intrasinus septum (or several septa) is not a reference point to determine the middle line since it is often displaced in one direction or another. MRI can help in an analysis of location of the cavernous segment of the ICA relative to the sella turcica floor. According to A. Rhoton, the mean distance between the ICA and the pituitary gland is about 2.3 mm. It should be noted that 25% of patients have demonstrated a medial displacement of the cavernous segment of the ICA towards the sella turcica [6, 19]. A similar situation — a medial displacement of the ICA — was observed in the patient in the case 2 (Fig. 3).

An increased risk of injury to the ICA upon transphenoidal surgery exists in patients with acromegaly due to changes in the anatomy of the nasal cavity and sphenoid sinus, a distance reduction between inner walls of the cavernous segment of the ICA from the right and left sides [12]. Upon reoperations or individual features, when the above mentioned reference points of the sphenoid sinus may be lacking, intraoperative navigation may be of great importance. The navigation system allows real-time determination of anatomical structures within the parasellar area.

The use of intraoperative ultrasonography can be helpful upon removing tumors from the cavernous sinus. Using an intraoperative Doppler probe enables quick and safe localization of the ICA prior to resection of the DM of the sella turcica floor, determination of the characteristics of blood vessels (the depth of the vessel location, its size, the blood flow velocity). Upon that the use of the ultrasonic probe, due to its small size, does not affect the visibility of the surgical wound [6, 16].

Massive bleeding, occurring upon injury to the ICA wall, is extremely difficult to stop, which can quickly lead to the development of the acute massive blood loss, hypovolemic shock, and coagulation disorders. In the event of profuse bleeding, coordinated work of the surgeon and an assistant is required. Clamping the common carotid artery in the neck can be used to stop bleeding temporarily. Upon ICA injury, the bleeding intensity is such that a single suction can not cope with the bleeding volume and the use of two surgical suctions is required. Surgeon’s manipulations should be directed to the earliest packing of the wound cavity with all available means for local hemostasis. However, excessively tight packing may cause injury to the visual and/or oculomotor nerves, compression of the carotid and/or basilar artery, which obviously occurred in the case 1.

From the standpoint of anesthesia care, there are two ways to solve the problem of the acute blood loss due to injury to the ICA. The first way is the preoperative preparation if the risk of intraoperative ICA injury is high. In this case, blood saving techniques are
<table>
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<tr>
<td>1. A 54-year-old female patient</td>
<td>Intra-, infra-, supra-, latero(D,S)sellar hormonally inactive pituitary adenoma</td>
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<td>Ischemia, hemorrhage to the cerebral cortex with the development of the dislocation syndrome. Death</td>
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<td>2. A 61-year-old male patient</td>
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<tr>
<td>3. A 40-year-old female patient</td>
<td>Intraseellar somatotropinoma (Fig. 7)</td>
<td>Incorrect identification of the middle line due to a change of the skull base anatomy caused by acromegaly</td>
<td>1500</td>
<td>15</td>
<td>Tight packing of the sella turcica cavity and sphenoid sinus with Surgicel Fibrillar, sponge, Tachocomb plates. Bio Glue was injected to the sphenoid sinus cavity</td>
<td>Anterior wall lesion of the left ICA in the anterior siphon knee, just below the ramus of the left ophthalmic artery (collateral blood flow is satisfactory)</td>
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<td>4. A 46-year-old male patient</td>
<td>Intra-, latero-(D,S)ellar prolactino-ma resistant to treatment with dostinex (Fig. 10)</td>
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<td>2500</td>
<td>50</td>
<td>Tight packing of the cavernous segment was performed with hemostatic Surgicel Fibrillar gauze and a hemostatic sponge, the sella turcica cavity was filled with Bio Glue</td>
<td>Injury was not determined immediately after surgery. FA in the anterior knee area of the right ICA was detected on the 8th day after the surgery</td>
<td>A stent-graft was placed</td>
<td>Discharged without augmentation of focal neurological symptomatology</td>
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used: hemodilution and installation of an apparatus for reinfusion of the autologous blood. Balanced infusion-transfusion therapy, provision of adequate venous approaches with a mandatory central vein catheterization for rapid correction of the circulating blood volume (CBV) and for performing infusion-transfusion therapy, and additional monitoring aimed at the hemodynamics control (control over the invasive arterial and central venous pressure) are required. A reserve of donor transfusion media, fresh frozen plasma, and packed red cells is also required. The second way is the direct correction of the acute massive intraoperative blood loss. Anesthesiologist’s manipulations are aimed first at eliminating the deficiency of the CBV volume of plasma coagulation factors, and only after that at replenishing the mass deficiency of circulating red blood cells and hemoglobin. Adequate and rapid replenishment of the CBV is the most important factor of the transfusiological approach. For this purpose we, at the NSI, have used crystalloid (saline solution — NaCl) and colloidal solutions (6 and 10% voluven, gelofusine) at the 3:1 ratio. This provides rapid achieving of normovolemia and adequate tissue oxygenation, provided that the hemoglobin level is not below 70—80 g/l. Transfusion of fresh frozen plasma is aimed at replenishment of the plasma, primarily labile (V and VIII), clotting factors to prevent the development of DIC and to provide adequate hemostasis. Transfusion of donor red blood cells is carried out only in the case of circulatory hypoxia and the hemoglobin level reduction less than 70—80 g/l. Transfusion media, fresh frozen plasma, and packed red cells are used after the occurrence of hemoglobin level reduction less than 70—80 g/l, which occurred despite performing hardware reinfusion of the autologous blood, and carried out to ensure adequate oxygen delivery to the tissues.

Stopping the bleeding should be immediately followed by angiography to localize a vessel injury site and to determine a subsequent treatment approach.

In our practice, the choice of an endovascular technique for treatment of this complication was dependent on availability of adequate collateral circulation, ICA tortuosity, and the type of vessel injury. The criterion for assessing adequate collateral circulation was consistency of the ACA and PCA confirmed by the cerebral angiography data. In our series of cases, endovascular treatment was required for 3 patients. ICA occlusion due to injury, detected by angiography, did not require additional endovascular treatment.

It should be noted that angiography does not always reveal a defect immediately after ICA injury. In these cases, it is necessary to repeat angiographic studies on the 7—8th days after operation.

Conclusion

Injury to the cavernous segment of the ICA upon transsphenoidal surgery is a rare, but potentially fatal complication. Thorough preparation for surgery — the study of neurovisualization data, improvement of the transsphenoidal approach technique under conditions of the anatomical laboratory — enables one to reduce risk for the development of this complication. Correct identification of the middle line is of great importance upon the endoscopic transsphenoidal approach, removal of pituitary and parasellar area tumors. This is especially important when removing tumors from the cavernous sinus cavity. In cases where the tumor is solid, it is reasonable not to delete the tumor portion adjacent to the ICA. In this situation, it is important to use various methods of neuronavigation (navigation systems, Doppler monitoring). Medical facilities, where endoscopic transsphenoidal surgery is performed, should be equipped with an endovascular operating room for emergency purposes in the case of injury to the ICA.

REFERENCES

The use of the endoscopic transsphenoidal approach is currently the most common method for removing many tumors of the sellar region. In this regard, the analysis of complications of this technique and improvement of an approach for their treatment is an extremely important task.

The article presents the results of treatment of sellar region tumors using the endonasal transsphenoidal approach in one of the largest series in the world (3,000 patients). This paper reports 4 cases of one of the most severe complications (injury to the cavernous segment of the internal carotid artery) as well as factors determining its occurrence. An approach for further treatment of these patients using the endovascular technique is considered, which apparently is essential and optimal. The decision to conduct endovascular intervention is made on the basis of angiography data that confirm injury to the internal carotid artery.

A surgical and anesthetic approach, when intraoperative injury to the internal carotid artery is detected, as well as preoperative preparation for surgery in patients with a high risk of this complication is described.

Present work thoroughly describes the methods used for endovascular treatment of injuries to the cavernous segment of the internal carotid artery as well as factors determining the choice of a particular method. Description of clinical cases is provided with ample illustrations.

In this article, the authors rightly emphasize the idea that endoscopic transsphenoidal surgery is advantageously carried out only in health care facilities, which are equipped with an endovascular operating room for emergency endovascular treatment of injuries to the internal carotid artery.

The structure of the paper is fully consistent with generally accepted principles of presentation of scientific material. The review of literature describes adequately the relevance and status of the issue. The article is provided with ample references to a number of domestic and foreign sources. Conclusions are fully consistent with aims of the work and with the results obtained.

The article can be recommended for publication in the press.

A. B. Klimov (Moscow)
Simultaneous Use of Direct and Endovascular Methods for Reconstruction of the Occluded Brachiocephalic Trunk


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An example of successful surgical treatment of a patient with progressive chronic cerebral ischemia due to an occlusion of brachiocephalic trunk and critical stenosis of the right internal carotid artery (ICA) over 85% is reported. The hybrid method of surgical treatment is described. The method included direct access to the neurovascular bundle on the right side, retrograde endovascular recanalization followed by angioplasty, and stenting brachiocephalic trunk during temporary occlusion of the distal internal carotid artery and simultaneous carotid endarterectomy on the right side. We provide an analysis of indications for each phase of the surgery, with allowance for the features of compensatory collateral circulation in the pool of occluded brachiocephalic trunk and possible complications of surgical treatment.

Keywords: brachiocephalic trunk, reconstructive surgery, hybrid surgery.

Oclusions of the brachiocephalic trunk are a rare pathology. In a series of ultrasound screenings, the brachiocephalic trunk occlusions were diagnosed in 20 out of 30,000 examined patients [5] and were detected in patients with manifestations of chronic cerebral ischemia in 1.5–2% of cases on average [12]. Atherosclerosis, nonspecific aortoarteritis, fibromuscular dysplasia, and intima dissection are the major risk factors for the development of occlusions [15]. Due to the well-developed collateral compensation of blood circulation in the chronically occluded brachiocephalic trunk, the clinical picture is frequently presented by progressive circulatory encephalopathy and vertebrobasilar insufficiency, as well as by signs of ischemia in the right hand [2, 3, 14, 15]. Ischemic stroke or transient ischemic attack (TIA) in the basin of the right middle cerebral artery (MCA) is revealed rather infrequently [7]. In this regard, the indications for surgical treatment in such cases essentially depend on the proposed surgical and anesthetic risks of surgical intervention. Despite the current progress in cardiovascular surgery, the use of open thoracic reconstructive surgery is still associated with the high incidence of complications and perioperative mortality; it is not considered to be justified in patients with chronic occlusions of the brachiocephalic trunk [2, 4, 15, 17, 20]. As endovascular surgery was developed, angioplasty and the stenting technique became the “Gold standard” of surgical treatment of stenosing pathology of the proximal aortic arch branches; the rate of technical success is more than 91%, and passability in the reconstructed area is more than 77% of cases during 2 years of follow-up [13, 19]. On the other hand, due to the low rate of successful recanalization (40%) and the risk of ischemic complications, the endovascular treatment of occlusions of the proximal aortic arch branches currently requires further study [1]. Hybrid approaches (open reconstructive interventions in the X-ray surgery room, additionally equipped for performing endovascular angioplasty and stenting under the X-ray optical control) have recently started to be used to improve the effectiveness of surgical treatment of chronic occlusions of the proximal aortic arch departments [8, 11]. This paper provides example of using direct and endovascular techniques to treat patients with chronic occlusion of the brachiocephalic trunk.

Case report

Patient S., 69 years old, was treated at the Burdenko Neurosurgical Institute in September 2009. When admitted to hospital, the patient complained of systemic headache, dizziness, unsteady gait, episodes of numbness and short weakness in the left limbs over the past six months with a frequency of 5–6 times per month, weakness and numbness in his right hand. The neurological status included mild pyramidal symptoms as left-sided hemiparesis and hemiataxia (4 points), increased tendon and periosteal reflexes on the left. Mild left-sided smoothness of the nasolabial fold was revealed. The patient demonstrated instability in Romberg’s test. He had low-amplitude nystagmus in extreme positions, vestibular ataxia, and grade 2 encephalopathy. The somatic status included mild pyramidal symptoms as left-sided hemiparesis and hemiataxia (4 points), increased tendon and periosteal reflexes on the left. Mild left-sided smoothness of the nasolabial fold was revealed. The patient demonstrated instability in Romberg’s test. He had low-amplitude nystagmus in extreme positions, vestibular ataxia, and grade 2 encephalopathy. The somatic status was characterized by coronary artery disease (functional class III), effort angina, hypertension stage II. Furthermore, the patient had chronic obstructive pulmonary disease and emphysema.
An objective examination showed that the right hand was pale, cold, no \textit{a. radialis} pulse on the right side was observed. Blood pressure was 70/50 mm Hg on the right, 140/90 mm Hg on the left. Duplex scanning revealed critical stenosis of the right internal carotid artery (ICA) over 85%, combined with occlusion of the brachiocephalic trunk and signs of the common carotid–vertebral steal syndrome (Fig. 1). Hemodynamically significant stenosis of the left subclavian artery in the 1\textsuperscript{st} segment and opening of the left vertebral artery were observed.

Selective angiography was performed after the patient had been admitted to hospital; the initial diagnosis was confirmed. A direct blood flow in the right common carotid artery (CCA) was found; it was provided by collaterals of the deep cervical arteries and retrograde blood flow in the right vertebral artery (see Fig. 1a).

Progressive chronic cerebral ischemia and TIA in the MCA basin were the reason for surgical intervention. In order to prevent possible complications, a decision was made to simultaneously use direct and endovascular techniques. The surgery was conducted by two teams of surgeons in an X-ray operating room and included three main stages. Taking into account the patient’s physical status and the need for neurodynamic monitoring, local regional anesthesia with blockade of branches of the right brachial plexus was selected as an anesthetic method. Multimodal neuromonitoring was additionally conducted; it included transcranial Doppler ultrasound (TCD) examination to detect the blood flow in the M1 segment of MCA on the right side and cerebral oximetry on the surgery side. Positioning of the patient is shown in Fig. 2a.

At the first stage, the open approach to the neurovascular bundle on the right side was performed. A 10-cm-long skin incision was made along the medial edge of the sternocleidomastoid muscle on the right side. \textit{M. platizma} was dissected. The medial edge of the sternocleidomastoid muscle was mobilized; the muscle was assigned laterally with a retractor. The facial vein was sutured and ligated. The internal jugular vein, along with the surrounding fiber, was displaced laterally. The CCA and its...

\begin{figure}[h]
\centering
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\caption{Occlusion of the brachiocephalic trunk (3) with formation of the syndrome of vertebral–subclavian and carotid–vertebral steal. a — compensation scheme of the collateral blood flow in the right CCA (1) and the subclavian artery (2) due to the retrograde flow from the right vertebral artery (4). The arrows indicate direction of blood flow; b, c — angiographic picture of brachiocephalic trunk occlusion.}
\end{figure}
bifurcation are isolated. Ripple in arteries was weak (colateral type). A dense atherosclerotic plaque in the area of CCA bifurcation, extending for 3.5 cm proximally to the CCA, was determined by palpation. The plaque was then densified diffusely in the external carotid artery (ECA) and ICA for 1.5 cm and 3.5 cm, respectively. The root of the hypoglossal nerve was located 3 cm above the bifurcation. ICA was isolated throughout 4 cm. The carotid body was coagulated and cut off. Traction sutures were placed on the CCA, ICA, ECA, and the superior thyroid arteries. During the test clamping of the CCA, the linear velocity of blood flow in the MCA on the right side was not reduced (80 cm/s); no focal symptoms were determined. It attested to good compensation of circulation in the basin of the occluded ICA and made it possible to prophylactically isolate the ICA from the bloodstream for a long period of time required for recanalization and stenting of the brachiocephalic trunk and following carotid endarterectomy. After the preliminary systemic heparinization (intravenous administration of 2,500 IU of heparin), the vascular clamps were superimposed on ICA, ECA, and the superior thyroid artery. A 7F introducer fixed with a tourniquet was inserted into the proximal lumen of the CCA through a small linear incision of its anterior wall (Fig. 2b).

At the next step, surgical interventions for recanalization and stenting of the brachiocephalic trunk were performed by the team of endovascular neurosurgeons.

After applying vascular clamps on the ICA and ECA, angiography was performed through the introducer; this showed the presence of occlusion of the brachiocephalic trunk from the aortic arch to the level of its discharge of the subclavian artery, while the latter was passable (Fig. 1b). A 4F catheter was inserted at the occlusion level through the introducer under X-ray control. The CoBra CiTop 6 vascular recanalization system (Ovalum) was also introduced through it. This device was used to establish a passage through the atheromatous masses to the aortic arch. Next, stepwise dilation was performed on a 0.14" microcatheter with 2.5×20 mm balloon catheter, and then with a 4×20 mm catheter throughout its length. A delivery system was positioned and the peripheral stent OmniLink 8×28 mm (opened at a pressure of 8 atm) on the Roadrunner 0.35" conductor was implanted at the occlusion level (Fig. 3a). According to control angiography, direct blood flow in the brachiocephalic trunk and right subclavian artery was restored. At this stage, endovascular surgery was completed. The CCA pulse emerged in the wound. The catheters and the introducer were removed; a clip was superimposed on the CCA.

At the third stage, right-sided direct carotid endarterectomy was performed according to the conventional procedure [21]. The linear incision on the CCA was distally extended along the anterolateral wall of the CCA from the point where the CCA introducer had been inserted (for 3.5 cm) with the transition to the anterior wall of the ICA (for 1.5 cm). A dense heterogeneous atherosclerotic plaque was detected; it had elements of decay that blocked up to 75% of the CCA lumen and up to 95% of the ICA orifice (for 1.5 cm distally from the bifurcation). Open endarterectomy from the CCA bifurcation (for 3 cm distally from it), from the ECA ostium (over 1 cm), and from the ICA ostium (over 1.5 cm) was performed. The arterial lumina were washed with normal saline solution. The remaining hanging small pieces of the plaque were removed with a mosquito clamp. A good retrograde flow from the ICA and mainline bloodstream from the CCA were observed. The arteriotomy opening was closed by continuous encircling stitch, using thread 7.0. Blood flow in the right MCA (during compression) was 70–80 cm/s. The clamps were removed from the arteries in the following order: ECA, CCA, ICA. After starting the blood flow, good pulsation of the arteries in the wound was observed. The total time of arterial clamping was 1 hr 48 min, including 15 min for reconstruction in the area of CCA bifurcation. Hemostasis was achieved.
A hemostatic gauze was applied on the region of arterial suture. The wound was closed with layered stitches until the active drainage to the vascular bundle. Local symptoms were not observed during arterial clamping. After the blood flow had been restored, the linear velocity of blood flow in the MCA increased to 110–120 cm/s.

Control intraoperative angiography showed good passability in the reconstruction zone of the right CCA bifurcation (Fig. 3b). In the postoperative period, the patient received antiplatelet therapy (75 mg of clopidogrel and 100 mg of aspirin daily). The patient noted regression of TIA, increased strength in the left extremities and right hand, as well as partial regression of vertigo.

The patient subsequently underwent routine endovascular angioplasty, stenting of the left subclavian artery, and open endarterectomy of the left vertebral artery ostium. During the 3-year follow-up, the reconstructed areas were passable; the bloodstream in the brachiocephalic arteries was anterograde and of the mainstream type. The patient was neurologically stable. No TIA was observed.

**Discussion**

The effectiveness of managing such a rare cause of chronic cerebral ischemia as occlusion of the brachiocephalic trunk considerably depends on the correct strategy of surgical interventions. This clinical case report presents the experience of curing a patient with the subcompensated course of cerebral ischemic disease along with advanced atherosclerosis. In these circumstances, surgical treatment was justified only with the minimal risk of surgical complications [16]. Endovascular recanalization followed by angioplasty and stenting of the brachiocephalic trunk was selected as the main reperfusion method. This minimally invasive technique associated with low perioperative risks has recently started to be used to restore blood flow in proximal aortic arch branches [1, 14]. The relatively low frequency of successful attempts of recanalization (40–50%), especially in cases of long chronic occlusions, limits the practical use of this intervention. Choice of the endovascular approach plays a great role in recanalization success: the closer approach to the occlusion, the more efficient intervention [1]. The transcarotid approach is optimal in patients with occlusions of the brachiocephalic trunk; however, it is associated with a high frequency of complications (cerebral embolism, CCA wall dissection, hemorrhage with developing hematoma of the neck). This approach is currently used in endovascular interventions rather rarely [9, 13]. In order to prevent complications of the conventional transcarotid approach in the described case report, open preparation of the neurovascular bundle on the right side followed by controlled retrograde catheterization CCA through a small arteriotomy incision of the distally occluded CCA was performed. This allowed one to achieve the most favorable conditions for endovascular recanalization of the brachiocephalic trunk. Direct carotid endarterectomy on the right side to treat 85% stenosis of the right internal carotid artery and suturing the arteriotomy incision allowed one to neutralize the drawbacks of the conventional transcarotid endovascular approach and to simultaneously execute planned reconstruction of the carotid arteries. This approach is justified in patients with advanced atherosclerosis, especially in the presence of stenotic lesions of the carotid pool and lower limb arteries (Leriche’s syndrome).

Another important problem in surgery of chronic occlusions of the brachiocephalic trunk is preventing ischemic complications (in particular, cerebral embolism), which requires careful preoperative examination of the collateral circulation [13]. According to the ultrasound and angiographic studies, brachiocephalic trunk

**Fig. 3. Results of the surgical intervention.**
a – condition after recanalization and stenting of the brachiocephalic trunk, b – control angiography of the ICA after its reconstruction.
occlusion causes various types of collateral compensation of the blood flow in the CCA, subclavian and vertebreal arteries [6, 10, 15]. Syndromes of subclavian–carotid and subclavian–vertebral steal with the formation of retrograde blood flow in the carotid and vertebral arteries are most frequently revealed [6]. Under these conditions, the risks of cerebral embolism and hemodynamic ischemic stroke are minimal, as proven by a series of successful endovascular recanalization with stenting of the aortic arch branches through the transfemoral approach [1, 12, 14].

Oclusions of the brachiocephalic trunk are much less frequently accompanied by the anterograde blood flow in the CCA due to carotid–subclavian steal [6]. In this case report, the patient had direct blood flow in the CCA and ICA supplied by the retrograde flow in the right vertebral artery and collaterals from the deep thoracic arteries (Fig. 1a). In such cases, there is an extremely high risk of ischemic complications due to cerebral embolism during recanalization of the brachiocephalic trunk [13]. This fact makes it necessary to ensure distal protection. When the endovascular approach alone is used, this is limited by technical difficulties and the need for using multiple approaches, which is not always feasible [1, 13]. Open access to the neurovascular bundle made it possible to temporarly “turn off” the ICA and ECA from the blood flow by applying vascular clamps on them. This was a simple and effective method for protecting against cerebral embolism. Multimodal intraoperative neuromonitoring of metabolism and cerebral blood flow (TCD ultrasonography and cerebral oximetry) to assess the tolerability of temporary occlusion of the ICA is important in this case [21]. Signs of cerebral blood flow compensation in the basin of the temporarily occluded right ICA in the reported case allowed one to conduct endovascular and direct stages of surgical interventions on the ICA clamped for 1 h 48 min without the development of neurological deficiency. Signs of sub- or decompenation of the cerebral blood flow could serve as a basis for using a temporary intraluminal shunt or distal protection against embolism (traps).

Surgical intervention under local regional anesthesia should be paid special attention. This method is absolutely indicated in patients with a history of severe somatic disorders (in particular, those with severe chronic obstructive pulmonary disease). Neurodynamic monitoring and verbal contact with the patient during the surgery allow one to properly interpret the neuromonitoring data in the case of subcompensation of the cerebral blood flow, when neurological deficiency may develop with a delay [18].

**Conclusion**

Direct and endovascular methods for surgical management of occlusive pathology of the brachiocephalic arteries are not always competing. The joint use of these approaches, with attention paid to the individual features of a patient, allows one to combine the advantages of each method, increase their efficiency, and improve the quality of surgical treatment of chronic occlusions of the brachiocephalic trunk.

**REFERENCES**


Migrating Choroid Plexus Papilloma of the Lateral Ventricle in an Infant: Modern Approaches to Surgical Treatment

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Choroid plexus papillomas (CPPs) are rare in adults and account for only 0.4–1% of all intracranial tumors, and although found in all age groups, they are primarily tumors of childhood – they account for 12–14% of all brain tumors in infants of the first year of life. The preferential localization of CPPs, up to 50% according to different series of studies, is the lateral ventricles of the brain.

A rare clinical case of an infant with "migrating" choroid plexus papilloma of the lateral ventricle is reported and current approaches to surgical treatment are reviewed.

Keywords: brain tumor in infants, surgery, choroid plexus papillomas, neurosonography, endoscope assistance, hydrocephalus.

Choroid plexus papillomas (CPPs) are rare in adults and account for only 0.4–1% of all intracranial tumors. Although they are found in all age groups, they are primarily tumors of childhood – they account for 12–14% of all brain tumors in infants of the first year of life [2, 8, 11]. CPPs are localized primarily in the lateral ventricles of the brain: up to 50% according to different series of studies [7, 12, 19].

The best strategy in CPP surgery is isolation of the tumor feeding vascular pedicle, its transection, and en bloc removal of the tumor [2, 18]. This strategy "justifies" extensive corticotomy upon a large tumor size and associated with this complexity of vascular pedicle isolation. Meanwhile, a cerebral cortex lesion over a large area, high hydrophilicity of the child's brain, small hemorrhages in the removed tumor bed increase risk for the development of subdural accumulations or progressive internal hydrocephalus (27 to 75%, according to the literature data [2, 14]), which require subsequent liquor drainage operations.

The planning of an optimal approach to the tumor and surgical strategy are usually performed on the basis of results of preoperative computed tomography (CT) and magnetic resonance imaging (MRI).

The aim of the present article is to describe a rare clinical case of "migrating" CPP of the lateral ventricle in an infant and modern approaches to surgical treatment.

Clinical observation

A 4-month-old girl. The 2nd uneventful pregnancy, birth in time, Caesarean section delivery. The first child of twins. Since her birthday, the girl was more somnolent than the second child, which has alarmed the mother. This was the reason to conduct an ultrasound (US) examination of the brain at the child's age of 3 weeks. A mass lesion in the cranial cavity was found. MRI confirmed the diagnosis of the tumor of the right lateral ventricle (Fig. 1a).

The absence of clinical symptoms and the small child's age were the reasons behind the case follow-up.

The control MRI of the brain one month later revealed migration of the tumor to the posterior horn of the right lateral ventricle; the tumor size increased slightly (Fig. 1b).

Upon a joint discussion with pediatric anesthesiologists, given the stable state of the child, the absence of clinical manifestations of the growth, small child's age, and a high risk of anesthesia, it was decided to abstain from neurosurgical operation. The case follow-up was recommended.

At the age of 3 months, the girl developed hyporexia; the motor development delay was observed: in the upright position she did not hold her head up; in the prone position she raised her head with an effort but did not hold it. The head circumference was 43 cm, the anterior fontanel was moderately tense and slightly bulging, the pattern of the subcutaneous venous network of the head was not intensified. Thus, the clinical symptoms were presented with the hydrocephalic syndrome (head circumference of 43 cm, tension of the anterior fontanel), motor development delay (not holding her head). The decision on surgical treatment was made.

The control MRI of the brain revealed a significant increase in size of the tumor and its migration into the anterior horn and body of the lateral ventricle (Fig. 1c).

Based on the latest results of the MRI examination of the brain, it was decided to remove the tumor using the transcallosal approach with endoscope assistance. Given the migratory nature of the tumor and in order to clarify
the localization of the tumor feeding vessel, Doppler neurosonography was performed immediately prior to surgery. A large feeding vessel – the choroidal artery passing inside the tumor – as well as migration of the tumor into the posterior and inferior horns of the right lateral ventricle were revealed (Fig. 2).

The neurosonography data changed the surgical approach – the approach to the tumor was performed transcortically through the parietal lobe to the ventricular triangle area using corticotomy up to 1 cm. The right lateral ventricle opened at a depth of 2 cm; the cerebrospinal fluid started to enter the wound under pressure; a pink colored growth, which looked like a typical choroid papilloma, was found in the right lateral ventricle (Fig. 3).

Removal of the growth was started using bipolar coagulation, suction, and micro-scissors.

Endoscopic inspection of the temporal horn revealed additional arteries coming to the tumor, which were also coagulated and cut off using micro-scissors.

Endoscopic inspection of the temporal horn revealed additional arteries coming to the tumor, which were also coagulated and cut off using micro-scissors. Thereafter, the residual tumor located in the posterior portion of the right lateral ventricle was easily removed. The tumor did not infiltrate the surrounding brain tissue. No residual tumor was found upon endoscopic inspection of the ventricular system. Control of hemostasis and the residual tumor presence was performed using endoscope optics 0, 30° (Fig. 5).

A contrast-enhanced MRI of the brain revealed complete removal of the tumor and the absence of complications (Fig. 6).
The child was discharged home in satisfactory condition. Catamnesis after 8 months showed no signs of intracranial hypertension.

**Discussion**


Over the past decades, diagnostics of brain tumors in children has become possible at the early stages of a disease due to the wide spread of brain imaging methods (neurosonography, CT, and MRI). Abroad and in Russia, neurosonography has been used widely as a method of primary diagnosis for all tumors of the ventricular system of the brain in infants [1, 13]. Publications relating to “migrating” CPPs have not been found in the available literature. Early diagnostics, implementation of microsurgical techniques, and improvement of a neuroanesthesiological technique have allowed neurosurgeons to operate on infants with brain tumors in the first year of life. The endoscope assistance technique, minimally invasive techniques in surgery of brain tumors in adults and older children have been described in detail in foreign publications [4, 15], but indications and application features for these techniques in infants have been described in the literature extremely poorly.

In modern publications, two features of choroid plexus tumors in infants, which complicate removal of the mass, are emphasized. The first feature is rich blood supply: the feeding arterial vessel may branch inside the tumor, which increases a risk of the intraoperative blood loss during removal. Some authors [6, 20] recommend superselective catheterization and embolization of afferents of choroid papillomas, but technical difficulties — a small bore of choroidal artery branches in infants — limit the widespread use of this technique. Moreover, removal
of CPP is not accompanied by profuse bleeding (until injury of the vascular pedicle supplying the tumor) in contrast to choroid plexus carcinomas.

The second feature is a large tumor size because of which the surgeon has to make extensive corticotomy in order to subsequently isolate and transect the vascular pedicle supplying the tumor, followed by en bloc resection of the tumor [10]. Extensive corticotomy and high hydrophilicity of the child’s brain increase the risk of brain tissue retraction and the development of tense subdural accumulations [2]. To avoid this, some authors [2] recommend the use of fibrin glue to close cortex lesions, but the effectiveness of this technique, to our opinion, is not convincing.

In this observation, Doppler neurosonography was performed immediately prior to surgery for clarification of tumor blood supply, which allowed not only to assess blood flow in the tumor but also to identify its migration to the posterior and inferior horns of the lateral ventricle. This enabled the surgeon to timely change the approach to the tumor. Endoscope assistance allowed us to remove the tumor through a minimally invasive approach and to avoid complications associated with the blood loss and traction of the child’s brain.

Conclusion

In the presence of a long feeding pedicle, migration of choroid papillomas within the ventricular system is possible even despite a large tumor size, which emphasizes the need for performing neurovisualization (ultrasoundography, MRI) immediately prior to surgical intervention to clarify the topography and blood supply of the tumor and to plan a surgical approach.

Endoscopic assistance in surgery of ventricular system tumors in infants enables identification of the feeding vessels at an early stage of surgical intervention, which allows reducing risk of intraoperative bleeding and surgery time as well as removing the tumor from the minimally possible approach (without extensive corticotomy and significant traction of the brain), performing failsafe hemostasis and thus reducing the risk for the development of tense subdural accumulations and progressive hydrocephalus.

REFERENCES

Commentary

The article by Prof. S.K. Gorelyshev et al. "Migrating choroid plexus papilloma of the lateral ventricle in an infant: Modern approaches to surgical treatment" presents an interesting clinical case of a brain tumor in a 3-month-old baby.

The use of intraoperative ultrasound neurovisualization and endoscopy allowed the surgeon to change the surgical approach to the tumor, thereby reducing inevitable surgical aggression of the initially planned, according to the preoperative MRI examination, approach. The use of the ultrasonic Doppler method is very helpful.

The simultaneous use of endoscopic and microsurgical methods significantly increases the degree of operation radicality and reduces its injury. The authors demonstrated the advantages of endoscope assistance in removing the choroid plexus papilloma of the lateral ventricle (endoscopic inspection of a residual tumor, microsurgical manipulations out of sight of the microscope with preservation of a low traumatic microsurgical approach).

Our experience also underlines the advantages of using endoscopic technology in treatment and diagnosis of tumors of the intraventricular localization. There may be very different variants of application: uniporal endoscope assistance in combination with microsurgery, as demonstrated in the present work, and in a variety of uni- and/or multiportal approach by means of transendoscopic surgery only.

Since 1996, we have operated on over 35 patients using the endoscopic approach for removal of intraventricular brain tumors. Upon that, the multi-portal approach has been used in 4 of 5 cases with choroid plexus papilloma, which allowed us totally transendoscopically, without craniotomy, to remove a mass lesion using several endoscopic ports.

Our experience allows us to speak about the advantages of the multi-portal approach in endosurgery, especially in severe cases. In this situation, multiportality allows one to use the required amount of tools, to control visually the situation in almost all parts of the brain ventricle and at different angles of view (e.g., in the opposite ventricle) as well as visualize panoramically the microtool tip relative to the brain structures with any power magnification and in the maximum brightness. For example, it is especially important during passing an endoscope through the narrow foramen of Monro. The use of ports of the same diameter is important to ensure the possibility for passing any tool through any port. All this greatly reduces the risk and dramatically increases possibilities of surgical intervention. Even bimanual manipulation is possible under certain favorable conditions (e.g., small intraventricular tumors) at some stages. These our data are consistent with the data of other authors [1–3].

Conclusion. The clinical case presented by the authors shows that the routine use of intraoperative ultrasound neurovisualization and an endoscopic technique is a prerequisite of neurosurgery for brain tumors, especially in children. We hope that this successful observation will stimulate further interest of contemporary Russian neurosurgeons in using minimally invasive and, in particular, endoscopic treatment methods, especially in this complex group of patients.

Dr. Med. Sci., Prof. A.A. Sufianov

REFERENCES

Medulloepithelioma, Ependymoblastoma and Embryonal Tumor with Multilayered Rosettes: Are they the Same Disease Entity?

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Medulloepithelioma is an extremely rare malignant tumor located predominantly in the supratentorial brain area. Microscopically, medulloepithelioma is characterized by epithelial structures that mimic the embryonic neural cells. Immunohistochemical analysis revealed that tumor cells are LIN28A immunopositive, and fluorescence in situ hybridization showed amplification of a miRNA cluster at 19q13. Presence of these aberrations gave grounds for assuming that medulloepithelioma, ependymoblastoma, and embryonal tumor with abundant neuropile and multilayered rosettes are the same disease entity.

Keywords: medulloepithelioma, ependymoblastoma, embryonal tumor with multilayered rosettes, miRNA amplification with 19q13.42, LIN28A.

Medulloepithelioma is a rare, highly malignant tumor arising in infants and invading predominantly the brain hemispheres. The tumor is classified as a primitive neuroectodermal tumor and belongs to Grade IV according to the WHO classification, along with CNS neuroblastoma, ganglioneuroblastoma, and ependymoblastoma [8].

Medulloepithelioma can also damage the ciliary body, retina, and the ophthalmic nerve, while enucleation of the ocular bulb gives a relatively favorable prognosis [3, 5, 11, 12].

The tumor consists of epithelial structured tissues (tubular, trabecular, and papillary) mimicking the embryonic neural cells.

The internal side of epithelium is bordered by the luminal surface with a plethora of adjacent mitoses, and the external limiting membrane. Medulloepithelioma can differentiate into the neuronal and neuroblastic, astrocytic, oligodendrogial, and mesenchymal cells; some authors have described melanin-containing medulloepithelioma: emergence of true ependymal (multilayer) rosettes similar to the ependymoblastic ones is another sign of medulloepithelioma [3, 4, 9, 12].

The current tumor classification [8], along with the data of neuropathomorphology experts [3, 4, 9, 12], recommends differentiating medulloepithelioma from ependymoblastoma, plexus carcinoma, immature teratoma, and atypical teratoid/rhabdoid tumor.

Emergence of medulloepithelioma is a rare event; therefore, description of each case is especially important, the more so, as the global literature data describe the morphological features only [2, 13], while molecular and genetic aberrations of the medulloepithelioma remain beyond examination.

The authors hope that the described case will make a major contribution to the insight into biological features of this neoplasm.

Case Report

A 22-month-old boy was admitted to the II Pediatric Unit of the N.N. Burdenko Neurosurgical Institute with a giant tumor of the left brain hemisphere. The child was born through spontaneous vaginal delivery at the 37th week of the first pregnancy without pathological findings. Body mass at birth was 2,750 g, height – 49 cm. The toddler’s motor development was slowed: he began to roll over at six months, creep and sit – at seven, walk – at 13.

The disease emerged when the boy was 19-month-old: he began to limp in his right leg; his body temperature was elevated to 38°C. Computed tomography examination (Fig. 1) revealed a giant tumor in his left brain hemisphere. The boy’s head circumference was actively increasing in the preceding three months. The symptoms of intracranial hypertension prevailed in the clinical pattern of the disease: progressive macrocrania (circumference of the patient’s head achieved 60 cm); progressive atrophy of the ophthalmic nerves in the fundus and blindness. The focal symptoms of the predominant lesion in the left hemisphere attracted our attention as well: restriction of the left gaze; central paresis of the VII nerve on the right side; tetraparesis up to 4 points on the left side, and up to 3 points on the right side; D>S reflexes; dissociations along the body axis; and coordination disorders with the pronounced progressive ataxia, along...
with the totally preserved limb motions. The giant tumor, reasonably well pseudopalisading the brain substance, was totally removed. After the histological verification, the boy and his parents got an oncologist’s advice to undergo the high-dose chemotherapy. Three months later, the boy died from the disease progression.

**Material and Methods**

Small fraction of the patient’s tumor material harvested intraoperatively and his blood were immediately frozen in liquid nitrogen and are stored at −80°C. The formalin-fixed and paraffin-embedded tumor was immunohistochemically examined using antibodies against: LIN28A (Polyclonal Antibody A177, #3978, Cell Signaling Inc., Boston, MA, USA) – dilution 1:50, exposure for 30 min at ambient temperature (37 °C is preferable); vimentin (Monoclonal Mouse Anti-Vimentin Clone V 9, Dako, Denmark); CK18 cytokeratin (Monoclonal Mouse Anti-Human Cytokeratin 18 Clone DC 10, Dako, Denmark); AE1/3 cytokeratin (Monoclonal Mouse Anti-Human Cytokeratin Clone AE1/AE3, Dako, Denmark); synaptophysin (Monoclonal Mouse Anti-Synaptophysin Clone SY 38, Dako, Denmark); neuron specific enolase (Monoclonal Mouse Anti-Human Neuron Specific Enolase Clone BBC/NC/VI-H14, Dako, Denmark); glial fibrillary acidic protein (Polyclonal Rabbit Anti-Glial Fibrillary Acidic Protein Cell Marque); nuclear marker of the INI1 gene deletion (Monoclonal Mouse Antibody — MRQ-27) – dilution 1:250, exposure for 30 min at ambient temperature; S-100 protein (Polyclonal Rabbit Anti-S100, Dako, Denmark); EMA (epithelial membrane antigen) (Monoclonal Mouse Anti-Human Epithelial Membrane Antigen Clone E29, Dako, Denmark) and alpha-fetoprotein (Polyclonal Rabbit Anti-Human Alpha-1 Fetoprotein Dako, Denmark).

Immunohistochemical examination with anti-LIN28A antibody was repeated: the manual examination revealed no expression in the medulloepithelioma cells, while both positive controls (ETMR – embryonal tumor with abundant neuropile and true rosettes, and germinoma) showed no expression. The examination using Lab Vision Autostainer 360 Thermo-Scientific immune stainer demonstrated bright positive expression of LIN28A in the cells of medulloepithelioma, ETMR, and germinoma.

Fluorescence *in situ* hybridization (FISH) was performed with the Vysis commercial probe (Abbott Molecular Vysis LSI N-MYC [2p24] Spectrum Green/CEP 2 Spectrum Orange Probe) and non-commercial bichromatic probe: FITC-labeled 634C1 probe to the 19q13.42 locus and the control digoxigenin-labeled 2659N probe against the 19p13 locus.

**Pathomorphological and molecular-genetic examinations**

All the intraoperatively harvested material (twelve paraffin blocks, except for the small tumor fragments frozen during the surgery) was examined. The histological examination showed a morphologically uniform malignant tumor with large necrotic areas. The tumor cells formed neuroepithelial structures: channels, cavities, and trabeculae resembling the embryonic neural tube. The tumor was abundantly supplied with true multilayer rosettes with mitotic figures (Fig. 2a, b) and deprived of micropile regions. The immunohistochemical examination revealed positive expression of LIN28A (Fig. 3) and vimentin; focal positive expression of AE1/3 and CK18 cytokeratins (Fig. 4); total nuclear expression of INI1 attesting to the lack of the INI1 gene deletion and excluding an atypical teratoid-rhabdoid tumor. No expression of GFAP (glial fibrillary acidic protein), S-100, synaptophysin, NSE (neuron specific enolase), EMA (epithelial membrane antigen), and alpha-fetoprotein was revealed. Fluorescent *in situ* hybridization de-
Monstrated cluster amplification of the 19q13 microRNA locus (Fig. 5), while no quantitative changes were revealed on chromosome 2 (balanced profile of chromosome 2) (Fig. 6).

**Discussion**

Medulloepithelioma is an extremely rare malignant tumor located predominantly in the supratentorial brain area. Only two cases of a medulloepithelioma were di-
agnosed at the Department of Pathological Anatomy, N.N. Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences in 2000–2013: the current case and the clinical observation in 2006. Meanwhile, primitive neuroectodermal tumors of the CNS have been diagnosed in 100 cases for almost 13 years; 19 of them were the primarily diagnosed embryonic tumors with abundant neuropile and multilayer rosettes ETMR (one of the largest world series collected in a single medical institution).

Some authors [2] believe that in case of recurrent ETMR, the tumor structure becomes more medulloepithelioma-like. Our experience confirms this observation [1]. However, the current case is a primary medulloepithelioma with biological features identical to those of ETMR: microRNA amplification at the 19q13 locus [6] and total LIN28A expression in tumor cells [7]. The aberrations found in the tumor genome allow us to follow S. Nobusawa et al. [10] and suppose that medulloepithelioma, along with ependymoblastoma and embryonal tumor with abundant neuropile and true rosettes, are the same disease entity.

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Treatment of patients with chiasmosellar area tumors is a serious problem of neurosurgery and neuroanesthesiology. This is due to the high prevalence of the disease (15–20% of all intracranial tumors [4]) and to localization of tumors in the area that is surrounded by the most important anatomical structures (internal carotid artery, cavernous sinus, chiasm, hypothalamus, III ventricle), the involvement of which may lead to serious complications during and after the surgery, including death, as well as to a variety of hormonal disorders and comorbidities associated with different types of adenomas, which represent most of pituitary tumors (85% of all pituitary tumors) [3, 4]. Approximately 55% of adenomas are associated with hypersecretion of single and in some cases several hormones [4]. The remaining 45% of adenomas develop symptoms that are determined by the influence of adenoma on the surrounding structures and the pituitary gland [4, 5, 43, 44, 49, 68].

Currently, the primary surgical treatment of chiasmosellar area adenomas is the transsphenoidal access via an endoscope – endoscopic endonasal transphenoidal adenomectomy (EETA), which is considered a minimally invasive procedure with adequate access and low complications rate. The use of EETA increases accuracy of surgeries and decreases their duration, but, more importantly, it expands surgery applicability to patients with developed clinical symptoms of the disease and the severe associated somatic pathology, including elderly patients, who require more careful anesthetic approach [3, 5, 31, 43, 44, 49, 68].

Anesthesia in transnasal neurosurgery is subject to the common rules of neuroanesthesiology, such as the preservation of adequate cerebral perfusion and oxygenation of the brain, ensuring normal conditions for the surgery procedure, adequate pain relief for the patient, hemodynamic stability, and quick recovery from the anesthesia for early neurological assessment of the patient [6, 8, 46]. However, apart from these general rules of anesthesia, there is some specificity in using EETA. First, it is the hormonal activity of pituitary tumors and their effects on the body as a whole [3, 43, 49]. Second, it is the effect of adenoma as a bulk on the pituitary and the adjacent structures (the mass effect of the tumor), and as a consequence, the possibility of occurrence of perioperative conditions, such as hypocorticism [36, 49] and hypothyroidism [4, 43, 48]. The mass effect can lead to compression and destruction of the pituitary gland and the development of hypopituitary failure, up to panhypopituitarism, intra- and postoperative acute adrenal insufficiency, disorders of the CSF dynamics and water-electrolyte imbalance [3, 4, 43]. Third, there are features of the surgical procedure (semi-sitting position of the patient with a possible risk of pneumocephalus and air embolism) [14, 49, 59].

Currently, there are few most significant problems in anesthesiology using EETA: condition of the somatic status of a patient caused by hormonal activity of the tumor or age, “difficult airway problem” (from anatomical changes in the airway leading to complications during application of a ventilation mask and during intubation of the patient), the choice of optimal anesthesia techniques, perioperative glucocorticoid support, the fight against postoperative nausea and vomiting, and postoperative pain syndrome. In this article, we will examine the first three problems in more details.

**Problem of the somatic status.** Under the influence of excessing hormonal activity of pituitary tumors, pathophysiological changes in the body are developed, which eventually lead to severe physical disability that is clinically manifested. Of greatest importance are the changes of the cardiovascular and respiratory systems, which are caused by prolonged hypersecretion of growth hormone (GH), adrenocorticotropic hormone (ACTH), and thyroid stimulating hormone (TSH) and are most clinically significant, since the changes in these systems lead to higher anesthetic risk.

**Hypersecretion of growth hormone.** Long-term GH hypersecretion eventually leads to severe endocrine, met-
abolish, somatic, and anatomical changes (gigantism, acromegaly) [4, 43, 49]. These patients are usually characterized by severe disturbance of the thyroid function [4, 48] that develops in 78% of cases [4] and is clinically manifested as hyper- and hypothyroidism, as well as severe disturbance of carbohydrate metabolism [4, 35, 48, 68]. The frequency of carbohydrate metabolism disorders in patients with prolonged hypersecretion of GH, which are based on disturbances of the central secretion regulation of insulin and glucagon, disturbances of protein-based glucose transport at post-receptor level and disturbances of the metabolically active form of insulin production, reaches 54% [4]. One of the expressed manifestations of carbohydrate metabolism disorder is diabetes, with insulin resistance as one of the characteristic features in patients with acromegaly [4].

A combination of metabolic and endocrine disorders with prolonged disease can lead to severe somatic disorders, the most important of which is the disorder of the cardiovascular system that occurs in approximately 50% of patients and is the main cause of mortality in the intra- and postoperative period, significantly increasing the risk during anesthesia [43, 49]. The most significant manifestations of the cardiovascular system dysfunction in acromegaly include arterial hypertension, left ventricular hypertrophy, cardiac arrhythmias, cardiomyopathy, and cardiomegaly. However, it should be noted that these changes are potentially reversible after successful surgical treatment [43, 49], although the size of the left ventricle does not always return to the normal after adenectomy due to interstitial myocardial fibrosis [4].

Hypertension under conditions of prolonged overproduction of growth hormone develops in about 25–50% of patients and is the major adverse prognostic factor that influences mortality [49]. Hypertension is difficult to be corrected during anesthesia and is apparently associated with the sodium and water retention in the body and increase in the circulating blood volume, as well as an increase in systemic vascular resistance (SVR) due to pathological thickening of the walls of arterioles in acromegaly patients [4, 43, 49]. The development of left ventricular hypertrophy is characteristic of patients with acromegaly and occurs in 50–70% of patients [49] due to hypersecretion of growth hormone or existing hypertension. This hypertrophy causes systolic and diastolic cardiac dysfunction and ultimately leads to a decrease in cardiac output [55]. A combination of cardiomegaly, cardiac hypertrophy, chronic tissue hypoxia, metabolic and endocrine disorders can lead to cardiomyopathy, which results in a significant decrease in cardiac output and tachycardia and can eventually cause circulatory decompensation, leading to severe chronic heart failure with pronounced systolic and diastolic dysfunction and an increased residual post-diastolic pressure in the left ventricle [28, 43, 49, 55, 56, 64]. Regardless of age, diffuse myocardial changes occur in patients with acromegaly and can lead to disruption of the blood supply (about 20%) and cardiac arrhythmia (42%) up to complete AV block [43, 49].

The respiratory system is also altered, along with pathological changes in the cardiovascular system in patients with hypersecretion of growth hormone. Besides the anatomical changes of the upper airway in patients with acromegaly, the terminal bronchioles are also altered. Their narrowing occurs due to edema and fibrosis, along with alveolar fibrosis. This leads to the difficulty in adequate gas exchange, despite the increase in total lung capacity and increase in "shunting of blood from right to left", pulmonary hypertension, and development of chronic cardiac and respiratory failure [34, 49].

Fatigue, weakness, a sharp decline in exercise tolerance associated with myopathy are usually detected. In patients with acromegaly despite in the increased muscle mass due to hypertrophy of muscle fibers [4]. Muscle weakness and fatigue are additional risk factors during the “difficult” mask ventilation, and endotracheal intubation and extubation, since such patients are subject to severe increase in hypoxia due to the rapid exhaustion of the reserves of the organism along with abnormal vascular system, endocrine and metabolic changes [49].

ACTH hypersecretion. Chronic overproduction of ACTH (Cushing's disease) is caused by the presence of a pituitary tumor or hyperplasia of adenohypophysis hormones, coupled with hyperactivity of the adrenal cortex. Overproduction of all three zones of the adrenal cortex is usually detected. Hyperfunction of zona fasciculata cells leads to cortisol hypersecretion; zona glomerulosa cells, to increased aldosterone production, which facilitates retention of sodium and water in the body and stimulates removal of potassium from the organism; zona reticularis cells, to increased adrenal androgen secretion [4]. Clinically, all of the above-mentioned pathophysiological processes lead to generalized disturbance of almost all organs and body systems [4, 43].

ACTH overproduction increases the levels of endogenous corticosteroids and activity of the renin-angiotensin system [21, 40]. Hydrocortisone stimulates the synthesis of angiotensin in the liver. Increased angiotensin activates the renin-angiotensin system [21, 40, 60]. Together with the elevated blood volume (aldosterone hyperproduction) and expressed total peripheral resistance (TPR) (50% of patients have diastolic blood pressure above 100 mmHg), all this leads to pharmacologically difficult-to-control arterial hypertension (in 85% cases), which is a major perioperative problem in these patients.

According to other authors, the main trigger of hypertension is glucocorticoids-stimulated Na⁺ influx in vascular smooth muscle cells. L. Kornel et al. [40] in their studies showed that glucocorticoid inhibition of phospholipase A₂ leads to the reduced synthesis of vasodilating prostaglandins. A. Sato et al. [61] in their studies have demonstrated that an active role in the development of difficult-to-control hypertension in patients with ACTH overproduction is played by the in-
creased synthesis of inositol triphosphate in vascular smooth muscle cells, resulting in increased sensitivity of angiotensin receptors. This leads to increased sensitivity to endogenous vasoconstrictors, such as angiotensin, adrenalin, and norepinephrine [60, 61]. The pronounced difficult-to-control hypertension together with secretion of excessive cortisol amounts leads to left ventricular hypertrophy; its combination with metabolic disturbances in the heart muscle can cause cardiac decompensation and chronic decreased cardiac output. Excessive potassium loss by cells due to redistribution with sodium causes changes in vascular reactivity and increased vascular tone. The potassium content in the muscle and the erythrocytes is reduced. These disorders lead to electrolyte-steroidal cardiomyopathy and the development of chronic heart failure [43, 49]. The myocardial function usually improves after complete removal of adenoma and normalization of hormone levels [49].

Patients with Cushing’s disease, as well as patients with overproduction of growth hormone, have significantly reduced physiological reserves of the organism. The combination of myasthenia gravis (one of the symptoms of Cushing’s disease), the pathologically changed cardiovascular system, and low exercise tolerance may result in rapid development of hypoxia, especially under “difficult mask ventilation” and “difficult intubation” with the decreased oxygen supply caused by reduction of functional residual lung volume and increased oxygen consumption. This situation requires careful pre-oxygenation in these patients and fast manipulation to ensure adequate ventilation [53]. Patients are also susceptible to gastroesophageal reflux disease, the risk of which is followed by aspiration of gastric contents into the airway, especially with the increased ventilation problems. Because of the high risk of aspiration and difficult intubation, fast actions and prompt beginning of anesthesia seem to be the safest [58, 72]. Furthermore, 60% of patients with overproduction of ACTH develop insulin resistant diabetes mellitus [4].

Adenomas with hypersecretion of TSH and prolactin. Adenomas with hypersecretion of TSH belong to the rarest type of hormonally active tumors (1–2% of all pituitary adenomas) [4, 49]. These tumors are most likely to manifest themselves as mass effect and are accompanied by significant blood loss when being resected due to invasive growth [3, 49]. In single cases, these tumors are accompanied by hyperthyroidism syndrome that is similar to manifestation of diffuse toxic goiter [43, 48, 49]. These patients, as well as those with overproduction of growth hormone and ACTH, are most likely to develop changes in the cardiovascular system, including sinus tachycardia, hypertension, seizures, or the occurrence of permanent atrial fibrillation. Over time, these patients develop chronic heart failure [32]. These patients are characterized by difficult anesthesia due to hemodynamic instability, which may lead to arterial hypotonia with sinus paroxysms or supraventricular tachycardia with the decreased cardiac output. Intra- and postoperative disruption of adequate coronary and cerebral perfusion can eventually occur [43, 49].

The presence of prolactinoma and prolactinemia usually does not impose any specific problems for anesthesia. However, there are several problems. First, these tumors may fail to have any specific severe symptoms for a long time and become large and even giant. In this case, the symptoms will manifest as the mass effect [3, 4, 49]. Second, having grown to a large size, the tumor may be a risk factor for massive blood loss due to frequent invasion of the cavernous sinus. Third, one needs to take into account the negative effect of drugs used to reduce prolactin blood level upon prolonged use. The commonly used dopamine agonists (bromocriptine, cabergoline, and pergolix) may cause nausea and orthostatic hypotension, which can be amplified by general anesthesia and hypovolemia. Prolonged use of dopamine agonists at high doses may cause cardiac valvular lesions (valvulopatia), which clinically manifest themselves as heart sounds and congestive heart failure [49].

The “difficult airway” problem. By definition proposed by ASA (American Society of Anesthesiologists), the “difficult airway” problem is the clinical situation when an experienced anesthesiologist faces difficulties in applying ventilation mask or intubating a patient using a conventional laryngoscope in more than 3 attempts or for over 10 minutes. During conventional anesthesia, the frequency of “difficult intubation” of trachea reaches approximately 3–18%. Difficulty in intubation may cause serious complications, in particular in case of failed intubation. In some cases of “difficult tracheal intubation”, an anesthesiologist may find himself in a situation when mask ventilation is difficult or infeasible; it is one of the most difficult situations in anesthesiologist’s practice. If an anesthesiologist predicts “difficult intubation” beforehand, it can significantly reduce the risks associated with anesthesia. There are various preoperative tests and classifications to make this prediction: classification of difficult intubation proposed by Lehane [2], Mallampati tests [23], modified Samsoon–Young classification [57], Cormack–Lehane classification during direct laryngoscopy [2], the Delikan test for occipital joint mobility, and the LEMON scale [2]. In addition to these tests and classifications, one can use linear Wilson’s discriminant analysis, which includes five variables: body weight, mobility of the head and neck, the movement range of the lower jaw, protruding teeth, and tongue size [70].

Unfortunately, the definition proposed by ASA, has some obvious disadvantages, since “difficult intubation” may be independent of the number of attempts or time. An experienced anesthesiologist who performs laryngoscopy may predict that the intubation will be difficult at the first attempt and within 30 s [2, 29, 63, 70].

There are four different definitions that are most important in determining the “difficult airway”: failed intubation, “difficult intubation”, “difficult laryngoscopy”,
and “difficult mask ventilation”. There are several different definitions of “difficult intubation”: repeated attempts of intubation, the use of a special device and alternative techniques, such as a MacCoy laryngoscope, laryngeal mask, bronchoscope, retrograde intubation, intubation using a rigid bronchoscope, video laryngoscopes, blind intubation, and intubation of a conscious patient [2, 29].

“Difficult mask ventilation” is less frequently discussed in the literature [69], although it is a virtually critical situation when combined with “difficult tracheal intubation” (approximately 0.1–15% of patients with “difficult intubation”) [37, 69]. Such a large variation in percentage of complex mask ventilation cases is attributed to the lack of universal systematization of the signs of its complexity and to the presence of various criteria to determine it [69], which may include obesity, age over 55 years, snoring, beard, grade IV changes in patient’s airway according to the Mallampati classification, pathological occlusion with protrusion of the mandible. The “difficult” mask ventilation is when an anesthesiologist is not able to support SpO2 at the level over 90% with FiO2 “difficult” mask ventilation is when an anesthesiologist cannot maintain the saturation level greater than 92% using 100% O2 and PPMV, and thus prevent reduction of blood saturation with oxygen [52]. According to the definition proposed by O. Langeron et al. [42], mask ventilation is considered difficult when an anesthesiologist cannot maintain the saturation level greater than 92% using 100% O2 and PPMV, even when the oxygen flow is equal to or greater than 15 L/min (even with two anesthesiologists participating). T. Yildiz et al. [71] defined difficult mask ventilation when there is no chest movement during ventilation, desaturation is observed, and oxygen is blown around the mask instead of entering the respiratory tract. S. Kheterpal et al. [38] proposed to consider difficult mask ventilation when it is impossible to achieve adequate oxygenation even when two anesthesiologists are involved in mask ventilation, when there is no capnograph trace on the screen, or there is neither chest motion nor chest contractions. The possibility of adequate mask ventilation is essential in the case of “difficult intubation”. If difficult mask ventilation is predicted, it is desirable to have ready-to-use fiber optic equipment in the operating room [19].

The “difficult airway” problem in anesthesiology during EETA is mainly related to the impact of prolonged hormonal activity of adenomas. Prolonged hypersecretion of GH stimulates generalized and local secretion of growth factors that cause increased production of mucopolysaccharides and collagen along with proliferation of chondrocytes, which ultimately leads to growth and thickening of soft tissues, cartilages and bones. The acromegaly condition develops under the influence of long-term GH secretion. Acromegaly is recognized as a serious cause of the “difficult airway” problem [2, 43, 51, 57, 62]. The prerequisites for it include: growth, swelling and thickening of the soft tissues of the mouth, tongue, laryngeal cartilages, periregphotic folds, excessive salivation, and chondrocalcinosis of the temporomandibular joints [30, 51, 58]. The complexity of tracheal intubation can also be affected by an enlarged thyroid gland, which can compress or displace the trachea [48]. When preparing a patient suffering from acromegaly for intubation, it is necessary to consider his past medical history, in particular the history of sleep apnea [23, 43, 49, 58]. This is a rare complication of acromegaly, but it attests a high risk of perioperative airway obstruction, which is 3 times higher than that in ordinary patients with acromegaly [58]. Anatomical changes in the respiratory tract are the major cause of sleep apnea in these patients [25, 58]. Severe thoracic kyphosis with or without chondrocalcinosis of joints (including mandibular) may cause difficult intubation and mask ventilation of a patient due to the inability to maintain the optimal position for the patient to perform these manipulations and the inability to properly open his mouth [29, 30, 43, 58].

Patients with ACTH overproduction develop dysplastic obesity, which is one of the risk factors for “difficult mask ventilation” and “difficult intubation”. The risk of “difficult intubation” in these patients is increased by 13% [43]. The increased volume of soft tissues of the upper airway causes their partial obstruction and reduced elasticity of the thorax. Excessive body weight, rapid physical fatigability, and metabolically active adipose tissue lead to increased oxygen consumption, along with the reduced functional residual capacity of the lungs and production of carbon dioxide. As a result, the patients exhibit more rapid fatigability and development of hypoxia during apnea. Thus, the onset of anesthesia, the supine position of a patient, and a pathologically elevated diaphragm (due to excessive visceral and abdominal obesity) cause a ventilation disorder, intrapulmonary shunting, and eventually arterial hypoxemia. Such patients are extremely prone to hypoxia, even in consciousness [25, 53]. The use of laryngeal mask is not recommended for these patients, since higher pressure is needed for ventilation because of the reduction of chest elasticity and its increased weight. To improve oxygenation and reduce alveolar collapse it is reasonable to use high positive end-expiratory pressure (PEEP) during mechanical ventilation (MV) [2].

Patients with prolonged TSH hypersecretion may also have anatomical constraints consisting in swelling of the soft tissues of the hypopharynx, which obstructs visualization of the larynx and glottis structures and increases traumaticity of soft tissues. Thyroid enlargement may also occur during extensive hyperfunction, when the thyroid gland compresses and/or displaces the larynx structures [4, 43, 48, 49].
When considering various intubation methods, there is no clear consensus about the superiority of one method over another one. Some authors recommend immediately conducting tracheostomy for patients with grade 3–4 airway changes [63], while the others [17] suggest fiber-optic intubation as a safer alternative. H. Schmitt et al. [62] considered intubation using a bronchoscope to be the method of choice in patients for whom “difficult mask ventilation” and “difficult intubation” were predicted. As authors have mentioned, the advantage of fiber-optic intubation is that it is less traumatic to the adjacent tissues, which indicates a very important point during intubation in patients with acromegaly. J. Benu-mof [19] noted that when predicting “difficult mask ventilation” and “difficult intubation”, the fiber-optic intubation could be performed on a conscious and spontaneously breathing patient. The author mentioned that the tracheostomy kit should be ready to use and should be applied when it is impossible to successfully intubate a patient using a bronchoscope. On the contrary, J. Messick and E. Laws [46] mentioned the “difficulties” associated with fiber-optic intubation in patients with acromegaly, especially in patients who have had difficulty in intubation with a conventional laryngoscope; those with developed changes in anatomy of the upper airway, heavily overgrown soft tissue and a large tongue; and also in the case when fiber-optic intubation was performed after repeated attempts of intubation with a rigid laryngoscope, which was responsible for the presence of blood in the upper airway after repeated intubation attempts and additional soft tissue swelling due to the inflicted injury [17, 23]. These authors suggested tracheal intubation using a laryngoscope with a sheath and long blade. Intubation in this case is carried out using the conventional laryngoscope, but a stiff guidewire was first introduced into the glottis instead of an endotracheal tube; the guidewire subsequently can be used to push or lift the epiglottis. After that, the guidewire is protruded behind the vocal cords and an endotracheal tube is introduced following the guide. In cases when the glottis cannot be visualized even if a rigid guidewire is used, the latter can be bent upwards (the “hockey stick” shape). Intubation in these cases is simplified because the tip of the curved wire is placed in the epiglottis, pushing it and moving into the trachea [39, 45].

In addition to the conventional flexible bronchoscope, in the case of “difficult intubation”, alternative fiber-optic devices (rigid bronchoscopes: Bullard, Up- sherScope, WuScope, Bonfils, Boedeker) are available and widely used. Despite the slight difference in design, all of them have common points, namely, the ability to provide quick imaging of the larynx without the need to align the laryngeal–pharyngeal axis (the axis between the larynx and the human eye). These bronchoscopes allow intubation, without straightening patient’s neck, which is a very important advantage in patients with large chordeomas of the skull base that spread to the craniovertebral junction, as well as when it is difficult to open patient’s mouth (e.g., in patients with chondrocalcinosis or temporomandibular joint arthroisis). These bronchoscopes allow successful intubation even when the mouth opening no more than 10 mm (Bullard) [9]. One can use Bonfils [20] and Boedeker (modification Bonfils) to intubate a patient with mouth opening so small that it is sufficient only to place a laryngoscope combined with an endotracheal tube. All of these bronchoscopes have another important advantage over the flexible bronchoscope: they are better in pushing the soft tissue of the mouth and throat due to their rigidity.

A laryngeal mask can be used during transnasal surgery [72]. The authors suggest the use of a laryngeal mask as an alternative to other methods listed above. They mentioned the simplicity of this technique, hemodynam-ic stability of patients, and minimal damage to the adjacent tissues, although this method is not welcome by surgeons, since the edge of the laryngeal mask may interfere with the surgeon during his or her manipulations. A laryngeal mask can be used throughout the anesthesia or as an intermediate step before successful intubation. When a gum elastic bougie is guided through the laryngeal mask, the bougie often reaches the trachea; so it can be used to insert a Pro-Seal endotracheal tube. The laryngeal mask can then be removed. The endotracheal tube can also be installed using a bronchoscope in this method. First, the bronchoscope is inserted in the laryngeal mask; a bougie is inserted under its control. Next, the bronchoscope is removed; an endotracheal tube is inserted using a bougie as a guide. In addition, a combination of a bronchoscope and a Pro-Seal endotracheal tube could be inserted through the laryngeal mask. Special laryngeal masks are produced for this purpose (Intavent Medical, UK). The laryngeal mask can be used when it is impossible to ensure adequate ventilation by the conventional mask and it is impossible to immediately intubate a patient with a Macintosh laryngoscope [29, 72]. The use of the laryngeal mask is not recommended for patients with Cushing’s disease due to the reduction of chest elasticity and its increased weight. More pressure is needed for ventilation; the PEEP control should be used to improve oxygenation and to reduce alveolar collapse during artificial ventilation.

Almost simultaneously with the introduction of laryngoscope to wide clinical practice, numerous attempts were carried out to enhance blade design and to improve visualization of the larynx. MacCoy laryngoscope is one of these laryngoscopes that could assist in “difficult intubation”. Its feature is the flexible blade tip: it allows better raising the extended epiglottis and the root of the tongue, which often obstruct the larynx during intubation of a patient with acromegaly using the conventional laryngoscope [45].

The technique using video laryngoscopy has recently been widely developed and applied to address the “difficult intubation” problem [24]. Despite their high cost,
video-laryngoscopes have a significant advantage over the conventional laryngoscopes as they increase the level of visual control and reduce injury rate, as well as increase the number of successful intubations. Due to the advance in digital engineering, new technologies have emerged, such as CMOS APS sensors (CMOS matrix — Complementary Metal Oxide Semiconductor — a photosensitive matrix based on CMOS technology). They allow one to visualize the structure of the larynx in sufficient details and reduce the need for the mandatory use of force to lift soft tissue, as they form a straight line from the pharynx to the eyes (the laryngeal–pharyngeal axis). One can use these devices to obtain good visualization of the oral cavity, larynx, and glottis even in patients with grade 3–4 according to the Cormack—Lehane classification. In addition, when the cable is connected to an external screen during the “difficult intubation” performed by two anesthesiologists, the second anesthesiologist can easily orientate him- or herself in the ongoing manipulations and assists more effectively [24]. Another important common feature of these devices, as well as different bronchoscopes, is the possibility not to extend patient’s neck during intubation and to intubate patients widely mouth that cannot be opened wide. The vast majority of videolaryngoscope models are the modified conventional Macintosh laryngoscope. The difference is that instead of a light source only, these laryngoscopes have a built-in camera on the blade or its combination with a light source. These videolaryngoscopes include: GlideScope, McGrath, Daiken Medical Coopdech C-scope vlp-100, Storz C-Mac, Pentax AWS, Berci DCI laryngoscopes, Video Macintosh Intubating Laryngoscope System (VMS), etc.

Another solution to the “difficult intubation” problem is the induction of anesthesia using inhaled anesthetics (oxygen with isoflurane or sevoflurane), with allowance for the short duration of their action [2]. In case of failed intubation, the inhalation anesthetic is not supplied and the patient is allowed to wake up [49]. Furthermore, when “difficult intubation” is predicted, retrograde intubation under local anesthesia can be used (while maintaining consciousness and spontaneous respiration). Retrograde intubation is shown to be an alternative in case of repeated unsuccessful attempts to intubate a patient by other methods, and these repeated manipulation caused bleeding and/or swelling of the soft tissues of the oropharynx, as well as in patients with limited neck mobility [2].

When any endotracheal intubation technique is used (even the most current ones), it the tracheostomy or cricothyromy equipment should always be within reach, especially when managing patients with acromegaly and grade 3–4 airway changes [66]. After tracheal intubation in these patients, the oral cavity, pharynx, and throat should be swabbed tightly to prevent blood from flowing into the stomach during surgery, which may stimulate postoperative nausea and vomiting and worsen lung ventilation [33].

Solving the “difficult airway” problem does not end after the intubation. One should be equally cautious both during intubation and extubation in these patients. Underestimation of the extubation risk prediction may lead to a real catastrophe (death), even after successful transnasal surgery. In most cases, extubation runs smoothly, without complications; however, according to the ASA, there can be problems associated with the “difficult airway” and ventilation disorder in about 7% of patients with the “difficult intubation” problem, ASA has developed a strategy for extubation of these patients with “difficult airway” [29, 47]:

1. Consideration of the risk balance for extubation of a conscious patient or under anesthesia.
2. Careful evaluation of factors that could impair the ventilation after extubation.
3. Development of a plan for immediate restoration of ventilation control if adequate ventilation was not achieved after extubation.
4. Consideration of the possibility of re-intubation the patient, if ventilation after extubation was inadequate.

The main task in this case is to avoid re-intubation of the patient, since re-intubation of such patients is usually difficult and dangerous. During re-intubation, a complex mask ventilation situation may arise: the patient may have an inadequate anesthesia recovery or the poorly passable upper respiratory tract. Patients with acromegaly have increased salivation, which can also impede breathing after the extubation. Furthermore, blood in the nasopharynx after transnasal surgery may disrupt adequate ventilation of the patient after extubation [43]. All these factors are complicated by the tendency to a rapid onset of hypoxia and hypoxemia in the patient. Such patients should be extubated in the operating room or in a special recovery room by experienced staff; all the necessary tools for emergency re-intubation should be used. Before extubation, one should inspect the airway using a laryngoscope to find possible swelling of soft tissues of the oropharynx and changes in the laryngeal inlet. Such patients can undergo a test: an anesthesiologist deflates the cuff of the endotracheal tube and monitors whether the airway is ventilated around the endotracheal tube. No ventilation may indicate swelling of the soft tissues around the endotracheal tube, which may lead to ventilation disorder after extubation. In such cases, one can consider tracheostomy or extubation along a rigid guidewire to facilitate the proposed re-intubation [2, 29, 47, 65].

Another threat in extubating patients with acromegaly is the post-extubation laryngospasm. It can develop after recurrent laryngeal innervation of the vocal cord nerves and their inadequate response to irritation, as well as vocal cord paresis, which can also disturb post-extubation ventilation [65].

All the aforementioned extubation problems are more common for patients with overproduction of growth hormone and developed acromegaly. Patients with Cushing’s disease have a lower risk of extubation.
problems. Morbid obesity, decreased chest elasticity, and reduced exercise tolerance are more significant factors in these patients [43, 49].

The problem of anesthesia selection for transnasal surgery. A broad range of acceptable anesthetics can be used in transnasal surgery; however, no definitive consensus on preferential use of inhaled or intravenous anesthetics has been reached [43, 49]. The problem of anesthetic selection for transnasal (as well as any other neurosurgical) operations is rather important. All anesthetic drugs affect the central nervous system to different extent (cerebral blood flow, cerebral metabolism, brain electrical activity, and intracranial pressure – ICP) [6, 65]. It was noted that most patients who underwent transnasal surgery did not develop increased intracranial pressure [46]. Anesthetic of choice for transnasal surgery anesthesia is an anesthetic that will have a beneficial effect on the central nervous system (and simultaneously reduce the cerebral blood flow and metabolic demand of the brain, reduce intracranial pressure, will not violate the regulatory mechanisms of cerebral blood flow) and will cause no noticeable systemic hemodynamic responses [65]. Systemic vasodilation, effect on the cardiovascular system, and effect on cardiac output are very important criteria for patients with pituitary adenomas. All inhaled and intravenous anesthetics that are applied during neurosurgical interventions cause respiratory and circulatory depression to a greater or lesser extent; hence, proceeding from these properties only, intravenous and inhaled anesthetics do not have any advantages over each other [49]. With respect to their effect on the central nervous system, there are significant differences [16, 67]. One must take into account such parameters as anesthesia controllability and time required for postoperative awakening, which is very important to provide early postoperative neurological assessment [6, 8, 13, 16, 18, 22, 27, 41, 43, 49, 54, 65, 67]. If all the aforementioned criteria are met, it will significantly reduce the risk of brain damage and the incidence of postoperative neurological complications.

Anesthetic effect on the cerebral blood flow is a crucial moment. An increase in the intracranial cerebral blood flow increases the blood volume and intracranial pressure (which may already be impaired because of the increased dynamics of cerebrospinal fluid in patients with large pituitary adenomas) [43, 49]. Anesthetics that expand cerebral blood vessels (cerebral vasodilators) increase intracranial pressure and cerebral blood flow [16, 67]. Inhaled anesthetics (such as halothane, isoflurane, sevoflurane, nitrous oxide) are cerebral vasodilators; they increase cerebral blood flow and disturb its autoregulation. Furthermore, they disturb the connection between brain metabolism and cerebral blood flow (which increases during deepening of anesthesia), and increase ICP [6, 16, 22, 65, 67]. These properties are expressed to the greatest extent in halothane [16]. There is no unanimous opinion about the use of nitrous oxide in neuroanesthesiology. On one hand, nitrous oxide does not significantly affect the hemodynamics, which is a positive feature. On the other hand, according to the literature, it also increases the cerebral blood flow and disturbs its autoregulation, although, it still is widely used as a primary anesthesia in neurosurgical patients [16, 67]. An unpleasant property of nitrous oxide is its ability to diffuse into any closed cavity filled with gas and to rapidly increase its volume, which increases the risk of complications during transnasal surgeries (e.g., pneumocephalus and air embolism) [14, 46, 59].

To some extent, the negative impact of inhaled anesthetics on the intracranial system can be reduced by moderate hyperventilation (which may cause hypocapnia and reduces the cerebral blood flow and intracranial pressure) [22]. A positive feature of inhaled anesthetics is that they ensure precisely controlled anesthesia. An anesthesiologist can easily vary the depth of anesthesia. A patient rapidly wakes up after the administration of inhaled anesthetics is canceled [43, 49].

Xenon, like other inhaled anesthetics, is an easily manageable anesthetic and ensures rapid awakening and rapid recovery of consciousness (in terms of time, it is comparable to propofol). Being a blocker of NMDA receptors, xenon exhibits a pronounced neuroprotective effect [10]. It also provides hemodynamically stable anesthesia [10, 11].

Intravenous anesthetics (barbiturates, propofol, and etomidate) are cerebral vasoconstrictors; they reduce cerebral blood flow and maintain the connection between brain metabolism and cerebral blood flow; they do not interfere with its autoregulation and reduce intracranial pressure [16, 67]. Barbiturates have been continuously and successfully used in neurosurgical patients; however, they have disadvantages associated with a significant impact on the cardiovascular system (expressed cardiac depression and hypotension), as well as unpredictable and prolonged duration of depression of consciousness after anesthesia, which makes it impossible to perform adequate dynamic neurological control [6, 8, 16, 49, 65, 67].

Etomidate is generally contraindicated for patients with pituitary disorders, despite the fact that it is a cerebral vasoconstrictor like barbiturates (but to a lesser extent) and has a minimal effect on the cardiovascular system. The main drawback of using it in patients with tumors of the chiasmosellar area of is ability to inhibit cortisol synthesis in the adrenal cortex, which may trigger the development of acute adrenal insufficiency, especially in patients with explicit or latent hypocortisolism [43, 49].

According to various authors [8, 13, 16, 54, 67], propofol is the most suitable drug for transnasal neurosurgical operations. It inhibits brain metabolism and reduces cerebral blood flow. Meanwhile, cerebral blood flow decreases regardless of blood pressure level. Propofol does not violate the connection between brain metabolism and cerebral blood flow, cerebral blood flow response to CO2, and its autoregulation. Propofol has an important advantage over barbiturates: high controllabi-
lity and short half-life (which ensures greater hemodynamic stability during a surgery), as well as the ability to ensure rapid wakening of the patient and early recovery of the adequate level of consciousness with the possibility of early neurological assessment [13, 16, 67].

Benzodiazepines reduce cerebral blood flow and cerebral metabolic needs, although to a lesser extent than barbiturates, etomidate, and propofol. Benzodiazepines also have a small hypotensive effect due to their effect on smooth muscle arterioles. Benzodiazepines cannot be considered as anesthetics because of the need to use high doses and long half-life; they are considered to be supplementary agents potentiating anesthetics or are used as premedication agents [41].

Opioids have no significant effect on cerebral metabolism and cerebral blood flow [6, 41]. Modern short-acting drugs are currently preferred (remifentanil). One can use short-acting narcotic analgesics in combination with sevoflurane or propofol to achieve precisely controlled anesthesia, greater hemodynamic stability, and earlier neurological assessment due to the reduction of anesthetic dose and the short half-life of an analgesic [43, 65].

Combined total intravenous anesthesia (TIVA) of propofol together with modern benzodiazepines, short-acting opioids, and regional bilateral anesthesia of the first and second branches of the trigeminal nerve (which are responsible for innervation of the nasal cavity and the sphenoid sinus) is promising for use in transnasal surgery [7]. The literature devoted to this problem is limited. Only few sources (two relating to our hospital) were found, although regional anesthesia based on blocking the trigeminal nerve branches at different levels is quite widespread in maxillofacial surgery and dental practice. This combination increases the manageability of anesthesia and intraoperative hemodynamic stability, reduces the negative effect of general anesthesia on the cardiovascular system by reducing the dose of general anesthetics and opioids, antihypertensive drugs; hence, it reduces the incidence rate of complications in the cardiovascular system and postoperative mortality. This technique is particularly reasonable for patients with severe cardiac pathology (both concomitant and induced by hormonal overproduction) [1, 7]. Theoretically, there are several options for the trigeminal nerve block, which are possible in transnasal surgery. They can be divided into different levels: proximal — blockade of Gasser ganglion, the middle one — blockade of the maxillary nerve, optic nerve, pterygopalatine node, and the distal one — blockade of terminal branches of the maxillary nerve, optic nerve, and anesthesia of the nasal cavity. The best option is to block the trigeminal nerve branches at the middle level, since both nasal mucosa and sphenoid sinus are anesthetized when this method is used. Bilateral blockade of the pterygopalatine node and maxillary nerve is one of the methods of median blockade. Blockade of Gasser ganglion and the nasociliary nerve is undesirable because of possible injury to large vessels and penetration of an anesthetic into the CSF space. It is also reasonable to use long-acting local anesthetics (to effectively combat postoperative pain), which have minimal vascular reactions (ropivacaine, bupivacaine). Intraoperative monitoring of the depth of anesthesia using BIS technology should be employed in such combined anesthesia to prevent unplanned recovery of consciousness [12, 15].

Conclusion

Problems described in this article (the physical status problem, the “difficult airway” problem, and the problem associated with selection if the optimal anesthetic technique), are interrelated and have not been fully resolved due to the lack of unified approach. Pathological changes in the cardiovascular and respiratory systems in patients with overproduction of growth hormone, ACTH, and TSH, along with the anatomical changes and possible “difficult” mask ventilation and intubation, often in conjunction with the old age of the patient, and reduced exercise tolerance in patients with metabolic and endocrine disorders may eventually lead to an abrupt decrease in the compensating capacity of the organism. As a result, there is a rapid development of the hemic and tissue hypoxia with chronic gas exchange abnormalities, reduced myocardial contractility and decreased cardiac output, which in turn leads to disturbance of the coronary and cerebral perfusion and significantly increases the anesthesia risks in these patients. Somatic changes are usually interconnected with disease duration. Such patients are prone to rapid decompensation of physical capacity of the organism and development of unstable hemodynamics (up to acute cardiovascular disease and death). These patients are more sensitive to the cardiodepressive action of anesthetics (which manifests as severe hypotension and resistant bradycardia) and poorly respond to therapy (in particular, at adequate bolus doses of anesthetics). All these features require further search for the optimal techniques for anesthesia management during transnasal surgeries.

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Szmuk P., Ezri T., Evron S. Prediction of difficult trachea intubation. From the Bronze Age to the Space Age. Inten Care Med 2008; 34: 222—228.

REVIEWS


Tumors of trigeminal nerve branches with extracranial spread are a rare pathology.

In modern literature, we found 62 cases of the tumors of trigeminal nerve branches with extracranial spread [22, 29, 31, 32, 34, 37, 39, 40, 46, 54, 61, 62]. Since this pathology is rare, we find it reasonable to provide a review of the literature focused on these tumors and intracranial tumors of the trigeminal nerve with an emphasis placed on the extracranial component.

In modern neurosurgery, the concept of “primary tumors of the trigeminal nerve” refers to the tumors originating from various anatomical sections of the trigeminal nerve: root, ganglion, and peripheral branches. Primary tumors of the trigeminal nerve are mostly benign slow-growing tumors of the nerve sheath (neurinomas and neurofibromas). Neurocytoma, neuroglioma, and ganglioneurinoma are the much less common histological types of tumors. According to the data reported by the world’s largest neurosurgical centers, primary trigeminal tumors are rare enough, ranging from 0.1 to 0.4% of all intracranial tumors, and from 1 to 8% of all intracranial neoplasms originating from the sheaths of the cranial nerves [9, 16, 23, 36, 45, 48, 50, 57, 63]. According to the reports of the N.N. Burdenko Neurosurgical Institute, these values are 0.3 and 5.8%, respectively [36]. Despite their rarity, schwannomas of the trigeminal nerve are the second largest type after the VIII nerve neurinomas. In turn, tumors of trigeminal nerve branches are even rarer, ranging from 5 to 11% of all tumors of the trigeminal nerve [36, 45, 50].

The disease frequently affects working age people (30 to 50 years) [1, 22]. Most of the available publications are presented by single cases; thus, it is evident that topographic-anatomical variations of the tumors of trigeminal nerve branches are very variable. This causes both the variety of clinical symptoms and regular difficulties in choosing a surgical treatment. Surgical solution to problems associated with this pathology remains one of the topical tasks of modern neurosurgery.

Classification of tumors of the nerve V

The history of studying the trigeminal nerve tumors is almost 200 years old. First neurinoma of trigeminal ganglion was described by R. Smith in 1836 (cited in [33]).

The anatomical features of the trigeminal nerve are responsible for a variety of topographic variants of tumors originating from it. Numerous attempts to classify the trigeminal nerve tumors have been made throughout the history of neurosurgery. It is generally accepted by most classifications that there are three types of these tumors: postganglionic root tumors; trigeminal ganglion tumors; and tumors of the peripheral branches.

It should be noted that all the known classifications of trigeminal nerve tumors did not make allowance for topographic features of the extracranial component (which is important for selecting a surgical approach) according to the preferential location of the tumor affecting several anatomical areas.

Morphology

Primary tumors of peripheral nerve sheaths are very rare; most of them are benign, slow-growing neoplasms. According to the current histological classification of soft tissue tumors by WHO (2003) and classification of CNS tumors by WHO (2007) [52], benign peripheral nerve sheath tumors include schwannomas, neurofibromas, and perineurioma. All the data available in English scientific literature mainly focus on trigeminal nerve schwannomas.

Schwannomas, neurofibromas, and perineuriomas develop from different tissue components, in accordance with their names. Schwannomas are composed of Schwann cells; neurofibromas are a combination of Schwann cells and fibroblasts, while perineuriomas originate from perineurium [18]. According to microscopy, there are two types of histostructure of schwannomas. The Antoni type A is represented by elongated bipolar cells with uncertain borders and elongated nuclei. These cells form the so-called “palisade-type structures” that include parallel rows of nuclei alternating with the acel-
lular zones of fibrous structure. The resulting pattern is known as Verocay bodies. The Anthony type B structures have reticular morphology; they are formed by loosely arranged cells with lymphocyte-like nuclei. The cytoplasm of these cells is optically empty due to xanthomatosis; thereby, yellow blotches are detected macroscopically in the tumor structure. Neurofibroma differs histologically from neuroma; above all, in terms of considerable amount of collagen fibers and presence of fibroblasts [3].

Each histological component of the benign peripheral nerve tumor both for the “basic” WHO units and those consisting of more than one component can be objectively identified by immunohistochemistry and electron microscopy. S100 protein, vimentin and epithelial membrane antigen serve as immunohistochemistry markers for Schwann cells, fibroblasts and perineurial cells, respectively [18, 28]. The peripheral nerve sheath tumors are frequently found in extremities (73.8%). The localizations can be arranged in terms of frequency of tumor occurrence as follows: the area of head and neck, torso; even rarer, the colon and other localizations [28]. Despite the relatively frequent finding of mitoses (up to 24% of cases), malignant peripheral nerve sheath tumors are extremely rare [28].

**Malignant peripheral nerve sheath tumors**

Malignant peripheral nerve sheath tumor (MPNST) is a malignant neoplasm belonging to the group of peripheral nerve sheath tumors. MPNST is also a general analogue of neurinomas and neurofibromas [14, 52].

Malignant trigeminal nerve schwannoma is an extremely rare disease of the CNS. Eighteen cases of primary malignant trigeminal schwannomas and only one case with malignant degeneration have been described in the English literature [5, 10, 13, 14, 19, 21, 26, 27, 35, 41–43, 58–60].

Malignant schwannomas may occur within neurofibromatosis type I (NF I). However, there is no correlation between the malignant trigeminal nerve sheath tumors and NF I, because only 1 of 18 patients had NF I [10, 56]. There is an opinion that these tumors can emerge after radiotherapy of the corresponding area, which was performed to manage other diseases [11, 13, 20, 38].

The mean time between the onset of symptoms and diagnosis was 2.8 months [10]. It should be noted that approximately 3/4 cases of malignant trigeminal nerve schwannomas developed in males (mean age, 47 years) (Table 1) [10].

**MRI and CT do not allow one to definitely differentiate the malignant trigeminal nerve schwannoma from its benign counterpart. The diagnosis may be suspected based on rapid growth of the tumor and earlier erosion of natural orifices of the skull base [56].**

Taking into account the rarity of malignant trigeminal nerve schwannomas, the treatment strategy for these patients remains unclear. The treatment of MPNST in other peripheral nerves includes radical tumor resection followed by radiation therapy [10, 44, 56]. Radiation therapy provides different results; however, it is frequently the only for treating such patients, since it is not always possible to totally remove the tumor, especially in the cases when the tumor infiltrates the adjacent structures. Chemotherapy has been applied in only one patient after surgery and radiotherapy [44]. Metastases of these tumors occur in perineurial spaces distally and proximally to the tumor. Hematogenous metastases to the lungs and bones are also possible; this was observed in 33% of cases [8, 35, 56]. About 50% of malignant schwannomas recur [8]. According to the data reported by different authors [17, 55], five-year survival rates range from 37.6 to 65.7%.

**Clinical presentation, diagnosis, and differential diagnosis**

In modern neurosurgery, the concept “primary trigeminal nerve tumors” refers to the tumors originating from various anatomical divisions of the trigeminal nerve: root, ganglion, and peripheral branches. Taking into account the anatomical features, clinical manifestations of tumors in different anatomical divisions of the trigeminal nerve are fundamentally different: cerebellopontine angle manifestations dominated in patients with nerve root impairment; tumor development in the trigeminal nerve ganglion is associated with symptomatic lesions of the medial portions of the middle cranial fossa, impaired sensation in the innervation area, and less frequently prosopalgia; the most polymorphic symptoms caused by extradural intracranial tumor spread appear when the nerve branches are impaired [1, 2]. There are two main groups in this variety of clinical symptoms: specific (trigeminal) and nonspecific. The first group includes such symptoms as numbness, paresthesia, weakness of masticatory muscles, corneal reflex inhibition, and facial pain. The incidence of these symptoms in patients with trigeminal nerve neurinomas is highly variable (Table 2) [4].

The second group of symptoms is considerably more extensive than the first one. It includes the following so-called “nonspecific” symptoms: headache, dysfunctions of other cranial nerves, eye proptosis, reduced vision, trophic cornea disorders, hearing loss, serous otitis, limited mouth opening with mandible deviation toward destruction, breathing difficulty and nasal bleeding, as well as cerebellar, pyramidal and paroxysmal symptoms, etc.

Diagnosis of trigeminal nerve tumors includes collection of past medical history, thorough clinical examination, CT, and MRI. Particular attention during clinical examination is paid to palpation of the emanation points of trigeminal nerve branches, studying sensitivity and function of the masticatory muscles, as well as corneal, superciliary, and mandibular reflexes.

During CT scanning of the brain, trigeminal nerve neurinoma gives an isodense or slightly hyperdense signal. Important radiological signs of trigeminal neuroinomas with extracranial spread can be detected in the bone window during CT scanning: erosion of the pyramidal
vertex and expansion of the natural orifices in the skull base (superior orbital fissure, oval and round orifices). The extended orifices have smooth edges.

MRI signs of trigeminal neurinomas include the isointense signal on T1WI, hyperintense heterogeneous signal on T2WI and FLAIR, and intense heterogeneous accumulation of contrast agent [47]. Cerebral angiography is performed relatively infrequently, mostly in patients with large neurinomas. Most often, the tumor does not have rich blood supply.

Differential diagnosis with meningiomas, metastases, hemangiopericytomas, chordomas, chondromas, vestibular schwannomas, and other brain tumors should be performed.

In terms of clinical presentation, cavernous sinus meningiomas may resemble the trigeminal nerve tumor. The most common symptoms of meningiomas of this localization is failure of the cranial nerves III, IV and VI; facial pains may also occur. Meningiomas appear on MRI T1WI as isointensive or slightly hypointensive structures. The tumor gives a signal with variable intensity on MRI T2WI: from isointense to moderately hyperintense one with respect to the medullary substance. Distinctive signs of meningiomas include the wide tumor base in the cavernous sinus; the long planar part of the tumor extending far away from the main tumor mass, the so-called dural tail, which occurs in 35–80% of cases; the presence of hyperostosis in the attachment area, and calcifications within the tumor [47].

Metastases to the skull base are frequently produced by prostate, lung and breast tumors. In the MRI T1WI and T2WI modes, metastases often give isointense and iso- or hypointense signals, respectively. Lesion borders are well visualized under contrast enhancement. Multiple foci also indicate the metastatic lesion.

Hemangiopericytomas are dense, well-bordered, vascularized mesenchymal tumors, which are almost always attached to the dura mater. Hemangiopericytoma can cause erosion of the skull base. These tumors are often very similar to meningiomas in terms of their X-ray pattern; however, they have neither calcifications nor hyperostosis. In a CT image, hemangiopericytomas look like a hyperdense extra-axial structure with peritumoral edema. These neoplasms frequently contain hypodense

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**Table 1. Published reports on primary MPNST of the trigeminal nerve**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Age, years/gender</th>
<th>Duration of symptoms before diagnosis, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50/M</td>
<td>6</td>
</tr>
<tr>
<td>C. Karmody, 1979 [35]</td>
<td>70/M</td>
<td>8</td>
</tr>
<tr>
<td>B. Liwnicz, 1979 [43]</td>
<td>53/M</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>67/F</td>
<td>—</td>
</tr>
<tr>
<td>F. Marou, 1986</td>
<td>49/F</td>
<td>1</td>
</tr>
<tr>
<td>Y. Horie and S. Akagi, 1990 [27]</td>
<td>18/M</td>
<td>2</td>
</tr>
<tr>
<td>S. Tegos and G. Georgoulis, 1997 [59]</td>
<td>66/M</td>
<td>1</td>
</tr>
<tr>
<td>D. DeRubeis, 1998</td>
<td>42/M</td>
<td>2</td>
</tr>
<tr>
<td>J. Stone and H. Cooper, 2001 [56]</td>
<td>71/M</td>
<td>Several months</td>
</tr>
<tr>
<td>J. Lee and H. Lee, 2001 [41]</td>
<td>35/M</td>
<td>1</td>
</tr>
<tr>
<td>R. Ueda and R. Saito, 2004 [60]</td>
<td>36/M</td>
<td>4</td>
</tr>
<tr>
<td>S. Chibbaro and P. Herman, 2008 [13]</td>
<td>40/F</td>
<td>Several months</td>
</tr>
</tbody>
</table>


**Table 2. Trigeminal symptoms**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Number of patients</th>
<th>Numbness (%)</th>
<th>Pain (%)</th>
<th>Paresthesia (%)</th>
<th>Weakness of masticatory muscles (%)</th>
<th>Corneal reflex (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. McCormick and A. Jacqueline, 1988 [45]</td>
<td>14 (120)</td>
<td>79% (30%)</td>
<td>36% (23%)</td>
<td>7% (6%)</td>
<td>29%</td>
<td>79%</td>
</tr>
<tr>
<td>M. Samii and M. Matteo, 1995 [50]</td>
<td>27 (190)</td>
<td>42% (10%)</td>
<td>17% (45%)</td>
<td>8% (46%)</td>
<td>—</td>
<td>(34%)</td>
</tr>
<tr>
<td>K. Yoshida and T. Kawase, 1999 [64]</td>
<td>27 (241)</td>
<td>48% (73%)</td>
<td>11% (25%)</td>
<td>11% (25%)</td>
<td>(4%)</td>
<td></td>
</tr>
<tr>
<td>A. Akhaddar and E. Mostarchid, 2002 [4]</td>
<td>4 (26)</td>
<td>(27%)</td>
<td>(35%)</td>
<td>(15%)</td>
<td>(4%)</td>
<td></td>
</tr>
<tr>
<td>R. Ramina and T. Mattei, 2008 [49]</td>
<td>17</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
<td>(4%)</td>
</tr>
<tr>
<td>A. Goel and T. Nadkarni, 1999 [24]</td>
<td>28</td>
<td>89%</td>
<td>46%</td>
<td>86%</td>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

*Footnote. The data published by different authors are given in parentheses.*
Heterogeneous accumulation of the contrast agent is observed when using contrast enhancement. In the T1WI MRI mode, the tumor gives a heterogeneous isointense signal. Angiography reveals a hypervascular neoplasm with abundant tumor blood vessels and extensive arteriovenous network.

Chordomas spreading to the cavernous sinus manifest themselves as failure of cranial nerves III, IV, V, and VI. When visualized on MRI, chordomas are characterized by variability in signal intensity in the T1WI mode. Spreading of a tumor into the medullary substance of the clivus results in substitution of the normal signal from the bone marrow fat with hypointense one. Moderate to severe signal hyperintensity is observed in the T2WI mode. Intense accumulation of the contrast agent is typical of chordomas. The sagittal and axial T1WI images show the involvement of neoplastic process of the sphenoid bone body and replacement of the bone structure with tumor tissue, which is characterized by low signal intensity.

Macroscopically, trigeminal nerve neurinoma is a soft, usually well-delimited encapsulated tumor. It should be mentioned that the tumor component located in the middle cranial fossa is always enclosed in the dura mater sheets of the lateral wall of the cavernous sinus (i.e. has interdural localization). It is noteworthy that extracranial components are always covered by capsule, which is the dura matter of the middle fossa or the perineural sheath [22].

Few publications have been devoted to trigeminal nerve branch neurinomas with extracranial spread. The largest series of this disease that has been described in the literature was made by an Indian neurosurgeon, A. Goel [22]. During 20 years (from 1989 to 2009), he performed 152 surgeries for trigeminal nerve neurinomas, 28 of which were regarded as trigeminal nerve branch neurinomas with extracranial spread. Tumors localized in the orbit only and not having their component in the middle cranial fossa were excluded from the study. Table 3 shows clinical manifestations of trigeminal nerve tumors with extracranial spread mentioned by the author in this article.

The author reported that spreading of the extracranial tumor over a long period caused “soft clinical symptoms”. Moreover, in some cases, patients paid no attention to the manifestation of early symptoms. As a result of these factors, most tumors were quite large at the moment of diagnosis.

Tumor sizes ranged from 27 to 78 mm in maximum dimension (the mean value was 52 mm). Important diagnostic criteria for CT included petrous apex erosion and extending orifices of the middle cranial fossa base (through which branches of the trigeminal nerve leave the cranial cavity): superior orbital fissure, round and oval orifices. Neurinomas of the first, second and third trigeminal nerve branches were observed in 4, 5 and 13 cases, respectively. In 6 cases, the tumor localized in the infratemporal/pterygopalatine fossa, but it was impossible to determine the nerve a tumor originated from. In 10 cases, tumor localized in all three compartments: the posterior fossa, middle cranial fossa, and extracranially (orbit, infratemporal and pterygopalatine fossa).

Most tumors were soft; in 22 cases, they had a moderate blood supply. Solid tumors were observed in 4 cases; those with abundant blood supply – in 2 cases. Polycystic neurinomas with necrotic masses were observed in 14 cases. The author was first to describe the presence of the liquid level in tumor cysts observed on MRI (2 cases); in one case, there was a calcification inside the neurinoma. Despite this variability of tumors, all neurinomas were separated by perineural/meningeal sheath from the adjacent structures. No malignant tumors were found [22].

In 1999, K. Yoshida and T. Kawase [64] reported 7 cases of trigeminal nerve branch neurinomas with extracranial spread among 27 trigeminal neurinomas that had been surgically cured by them in 1974–1999. Neurinomas localized only in the orbit were excluded from this study. In three cases, the tumors manifested as hypoesthesia; in 2 cases, as facial pain in the corresponding innervation zone and exophthalmos; and in one case, as hearing impairment and tinnitus. Past history of the disease ranged from 9 days to 7 years (mean: 26 months). It should be noted that in one case, a 25-year old patient sought medical help 9 days after the onset of hypesthesia. Tumor size ranged between 17 and 70 mm (average 48 mm). In 5 cases, neurinoma consisted of the solid component, and in 2 cases it was mixed.

In 2008, R. Ramina and T. Mattei [49] published their own experience the treatment of 17 trigeminal nerve neurinomas over 20 years; 6 of those were with extracranial spread. Other authors [4, 29, 31, 32, 34, 37, 39, 40, 46, 54, 61, 62] described only sporadic cases.

**Surgical treatment**

Today, there is no universal strategy of surgical treatment of trigeminal nerve tumors with extracranial spread. Surgeons use very diverse surgical approaches.

A. Goel [22] used zygomatic osteotomy in combination with basal temporal osteotomy in 12 cases. For tumors spreading to the orbit, zygomatic osteotomy was extended up to the frontal process of the zygomatic bone.

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**Table 3. Clinical manifestations of trigeminal nerve tumors with extracranial spread (n=28) [22]**

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness and/or tingling</td>
<td>25</td>
</tr>
<tr>
<td>Facial pain</td>
<td>13</td>
</tr>
<tr>
<td>Difficulty in chewing:</td>
<td></td>
</tr>
<tr>
<td>due to atrophy of the temporal/chewing muscles</td>
<td>24</td>
</tr>
<tr>
<td>due to tumor bulging to the oral cavity</td>
<td>5</td>
</tr>
<tr>
<td>Exophthalmos (main symptom)</td>
<td>7</td>
</tr>
<tr>
<td>Earache</td>
<td>2</td>
</tr>
<tr>
<td>Lack of trigeminal symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms for the other cranial nerves</td>
<td>11</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>2</td>
</tr>
</tbody>
</table>
Lateral orbitotomy was applied in 4 cases. In most cases, temporal and other muscles of infratemporal fossa were atrophied. Preliminary lumbar drainage gave 1.5–2 cm extra space and additional angle of about 20° of surgery attack for manipulation in the infratemporal and pterygopalatine fossae. The middle cranial fossa base was resected to expose the tumor in the infratemporal, pterygopalatine, and middle cranial fossae. The dura mater was then dissected on the outer wall of the tumor, reducing its volume. The author warned about the risk of damaging the meningeal/perineural layer on the inner wall of the tumor, since the internal carotid artery and cranial nerves of the cavernous sinus may localize behind it. The trigeminal nerve neurinomas include not all the nerve fibers. The author recommends making intracapsular resection of the tumor via blunt dissection with an ultrasonic aspirator, which allows one to keep the trigeminal nerve fibers not involved in the tumor stroma. A. Goel [22] reported on radical and partial resection of the nerve V neurinoma with extracranial spread in 20 and 8 cases, respectively. The author also noted that in 2 out of 8 cases of subtotal resection, the tumor was inadvertently left in the posterior fossa. In two other cases, neurinomas were plexiform; thus, radical resection was infeasible. The follow-up period ranged from 6 months to 19 years (mean time: 90 months). In 4 (14%) cases, continued tumor growth was observed, and 2 patients were reoperated. In both cases, complete tumor resection was not achieved at the first step. In two other cases with continued tumor growth, the tumor was completely removed during the first surgery. In postoperative period, none of the patients underwent radiosurgery and/or radiotherapy. Numbness and atrophy persisted in all cases, where these signs were revealed prior to the surgery. Corneal opacity developed in the late postoperative period in only one patient [22, 24].

K. Yoshida and T. Kawase [64] used frontotemporal, zygomatic infratemporal and combined (zygomatic infratemporal and anterior transpyramidal) approaches twice each, and the orbitozygomatic infratemporal approach once. In 5 cases, tumors were removed radically; in 2 cases, patients underwent subtotal tumor resection. In cases of subtotal resection, tumor exhibited continued growth and required reoperation. In the postoperative period, anesthesia of the corresponding innervation zone developed twice; ophthalmoplegia and enophthalmos were observed in one case.

R. Ramina and T. Mattei [49] recommended using the following surgical approaches for neurinomas with extracranial spread:

1. The extradural transmaxillary approach for neurinomas mainly localized in the extracranial space with insignificant intracranial spread. The authors sometimes combined this approach with the extradural frontotemporal one.

2. The frontotemporal intradural approach for neurinomas mainly localized in the middle cranial fossa with insignificant extracranial spread.

3. The presigmoid approach combined with the transmaxillary one to resect neurinomas spreading to the posterior and middle cranial fossae and to the extracranial space.

The role of radiosurgery/radiotherapy in treatment of nerve V tumors

Despite the fact that resection is the main method for curing trigeminal tumors, the risk of disability is still high [25, 30, 36, 45, 53]. According to some authors [6, 15, 23, 33, 45, 50, 51], new neurological deficit after surgical removal occurs in 13–86% of cases. Due to the rarity of this pathology, most surgeons do not have sufficient experience, and radical resection of this tumor remains a great challenge for them [7, 12, 45, 48, 50, 53, 63]. Another reason is close localization of the tumors to the cranial nerves and vessels.

In 2007, T. Hasegawa et al. [25] reported on treatment of 42 trigeminal neurinomas using Gamma Knife. In 20 cases, radiosurgery was used as primary treatment. The remaining patients were operated on earlier. Complete and partial remission was achieved in 11 and 54% of cases, respectively. In 22% of patients, resection stabilized the disease. In 14% of cases, treatment failed: the continued tumor growth after 12, 15 and 30 months was observed in 3 patients; facial pain and brain edema emerged 17 and 30 months after the radiosurgery in 2 cases. The five-year and 10-year tumor growth control rate was 84%. It was 69% for large tumors (>15 cm³) and 88% for small ones (<15 cm³). The clinical symptoms regressed in 40% of patients and remained unchanged in 46%, while the negative trend was observed in 14% of cases.

In 2009, H. Kano et al. [33] reported on treatment of 33 patients using the Gamma Knife device. Eleven patients were operated on previously. The tumor completely eliminated after radiotherapy in 6% of cases. The tumor decreased by more than 50% and 0–25% of its original size in 45 and 36% of patients, respectively. In 12%, the treatment was considered to be unsuccessful. All patients with continued tumor growth underwent repeated radiosurgery. One patient after two radiosurgery sessions was reoperated, since the tumor continued to grow. The disease-free survival rate after 1, 5 and 10 years were 97%, 82% and 82%, respectively. The authors pointed out that such factors as female gender, small tumor size (<8 cm³), and neurinomas localized in the posterior fossa improved the favorable outcome.

Conclusion

Hence, due to the rarity of trigeminal nerve branch neurinomas and neurofibromas with extracranial spread, the treatment strategy for these tumors has not been developed yet. Because of the nature of these tumors and their spread to the orbit, sinuses, infratemporal fossa, surgical treatment needs to be developed, which would allow one to remove the intra- and extracranial tumor portions with minimal damage.
REVIEWS

REFERENCES


Topics to be covered in our next issue:

- Neuroanatomical foundations of traumatic coma: clinical and magnetic resonance correlation
- Evidence-based neuro-resuscitation: What comes next?
- An existential-phenomenological approach to understanding consciousness and management of unconscious patients