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

**Topics to be covered in our next issue:**

- Neuroimaging and navigation in treatment of spine tumors
- Clinical recommendations for traumatic brain injury (Part 2)
- Hyponatremia in neurosurgical patients
The aim of the study was to assess the capabilities of diffusion kurtosis imaging (DKI) in diagnosis of the glioma proliferative activity and to evaluate a relationship between the glioma proliferative activity index and diffusion parameters of the contralateral normal appearing white matter (CNAWM). Material and methods. The study included 47 patients with newly diagnosed brain gliomas (23 low grade, 13 grade III, and 11 grade IV gliomas). We determined a relationship between absolute and normalized parameters of the diffusion tensor (mean (MD), axial (AD), and radial (RD) diffusivities; fractional (FA) and relative (RA) anisotropies) and diffusion kurtosis (mean (MK), axial (AK), and radial (RK) kurtosis; kurtosis anisotropy (KA)) and the proliferative activity index in the most malignant glioma parts ($p<0.05$). We also established a relationship between the tensor and kurtosis parameters of CNAWM and the glioma proliferative activity index ($p<0.05$). Results. The correlation between all the absolute and normalized diffusion parameters and the glioma proliferative activity index, except absolute and normalized FA and RA values, was found to be statistically significant ($p<0.05$). Kurtosis (MK, AK, and RK) and anisotropy (KA, FA, RA) values increased, and diffusivity (MD, AD, RD) values decreased as the glioma proliferative activity index increased. A strong correlation between the proliferative activity index and absolute RK ($r=0.71; p=0.000001$) and normalized values of MK ($r=0.8; p=0.000001$), AK ($r=0.71; p=0.000001$), RK ($r=0.81; p=0.000001$), and RD ($r=-0.71; p=0.000001$) was found. A weak, but statistically significant correlation between the glioma proliferative activity index and diffusion values RK ($r=-0.36; p=0.014$), KA ($r=-0.39; p=0.007$), RD ($r=0.35; p=0.017$), FA ($r=-0.42; p=0.003$), and RA ($r=-0.41; p=0.004$) of CNAWM was found. Conclusion. DKI has good capabilities to detect immunohistochemical changes in gliomas. DKI demonstrated a high sensitivity in detection of microstructural changes in the contralateral normal appearing white matter in patients with brain gliomas.

Keywords: diffusion tensor, diffusion kurtosis, glioma, malignant, proliferative activity.

Abbreviations
AD — axial diffusion
AK — axial kurtosis
HGG — high-grade glioma
LGG — low-grade glioma
DKI — diffusion kurtosis imaging
DTI — diffusion tensor imaging
ZOI — zone of interest
KA — kurtosis anisotropy
CNAWM — contralateral normal appearing white matter
RA — relative anisotropy
RD — radial diffusion
RK — radial kurtosis
MD — mean diffusion
MK — mean kurtosis
FA — fractional anisotropy

Proliferative activity of gliomas and their degree of malignancy, localization, size and spread of the tumor, completeness of the tumor’s surgical removal, as well as a patient’s age and neurological status are very important for the disease prognosis and survival [1]. Several methods have been developed to date to assess proliferative activity of the tumors [2, 3] with Ki-67/MIB-1 labelling index (Ki-67/MIB-1 LI) being the most reliable and the most common way of assessing mitotic activity [4].

A review [5] of 16 works, which included 915 patients, demonstrates statistically significant increase in Ki-67/MIB-1 LI with increasing grade of brain astrocytomas. For astrocytomas, Ki-67/MIB-1 LI values above 10% are considered to be indicative of high malignancy potential [5]. Statistically significant correlation has also been demonstrated for Ki-67/MIB-1 LI and prognosis, survival and tumor recurrence [5—8]. Furthermore, Ki-67/MIB-1 LI is believed to be a more important marker for gliomas prognosis than their histologically defined tumor grade (WHO grade) [8, 9].

The data of standard MRI with intravenous contrast display good correlation with Ki-67/MIB-1 LI values: gliomas that accumulate the contrast medium are characterized by average Ki-67/MIB-1 LI values up to 8.1%, while the tumors without contrast enhancement typically have values of about 2.0% ($p=0.0007$) [10]. However, determination of Ki-67/
and 1 subependimal giant cell astrocytoma. The group of oligoastrocytomas. Grade I gliomas included 2 gangliocytomas and 3 grade I gliomas). Grade IV gliomas included 10 (HGG) (11 grade IV gliomas and 13 grade III gliomas) and 23 values of the tumors were confirmed by histopathological and stereotactic biopsy within 1—2 weeks after the DKI. For all study. All patients underwent surgical removal of the tumor or patients with history of other cancers were excluded from the study. All patients underwent surgical removal of the tumor or stereotactic biopsy within 1—2 weeks after the DKI. For all patients, the morphological diagnosis and Ki-67/MIB-1 LI value in a tumor using the standard MRI technique is a rather challenging task. A number of published papers [7, 11—19] is devoted to a correlation between diffusion tensor MRI (DTI) parameters, namely mean diffusion and fractional anisotropy, and Ki-67/MIB-1 LI.

Diffusion kurtosis imaging (DKI) is a novel neuroimaging technique, which has been gaining traction in the recent years and demonstrates higher sensitivity in characterization of the brain tissues microstructure under normal and pathological conditions. DKI can be used to quantify a number of parameters: • mean, axial and radial kurtoses (MK, AK and RK), which describe resistance to molecular transport (SK, mean resistance, AK, resistance along the axons, RK, resistance in the plane perpendicular to the axons, respectively); • kurtosis anisotropy (KA), which describes the homogeneity of resistance to molecular transport in different directions; • mean, axial and radial diffusion (MD, AD and RD), which describe flow rates of molecules (MD, average flow rate, AD, flow rate along the axons, RD, flow rate in the plane perpendicular to the axons, respectively); • fractional and relative anisotropy (FA and RA), which describe the uniformity (isotropy) of the molecular flow rate in different directions.

There are no papers in Russian and foreign literature on the use of DKI in the diagnosis of the gliomas proliferative activity. Our paper is the first publication describing an attempt to correlate Ki-67/MIB-1 LI proliferative activity index with gliomas DKI parameters; we are also the first to study a relationship between diffusion kurtosis parameters of the contralateral normal appearing white matter (CNAWM) and gliomas Ki-67/MIB-1 LI values. Our work is also the first one to use a number of additional diffusion tensor parameters (axial and radial diffusion, relative anisotropy) in the study of gliomas Ki-67/MIB-1 LI values; the authors of the previously published papers mainly used average diffusion and fractional anisotropy.

Material and Methods

The study was approved by the ethics committee of the Burdenko Neurosurgical Institute. All patients signed a written informed consent form to participate in the study. The study included 47 patients with supratentorial gliomas of the brain. These patients were diagnosed and treated at the Burdenko Neurosurgical Institute. All gliomas were newly diagnosed, with no prior surgery, radiation or chemotherapy. Patients with history of other cancers were excluded from the study. All patients underwent surgical removal of the tumor or stereotactic biopsy within 1—2 weeks after the DKI. For all patients, the morphological diagnosis and Ki-67/MIB-1 LI values of the tumors were confirmed by histopathological and immunohistochemical studies.

The study included 24 patients with high-grade gliomas (HGG) (11 grade IV gliomas and 13 grade III gliomas) and 23 patients with low-grade gliomas (LGG) (20 grade II gliomas and 3 grade I gliomas). Grade IV gliomas included 10 glioblastomas and 1 gliosarcoma. Grade III gliomas included 12 anaplastic astrocytomas and 1 anaplastic oligoastrocytoma. Grade II gliomas included 18 diffuse astrocytomas and 2 oligoastrocytomas. Grade I gliomas included 2 gangliocytomas and 1 subependimal giant cell astrocytoma. The group of patients included in our study consisted of 29 men and 18 women; the average age of the HGG patients was 43.8±14.7 years, the average age of the LGG patients was 37.7±9.6 years.

DKI was performed on MRI scanner with 3.0 Tesla magnetic induction, using echoplanar spin echo (SE-EPI) pulse sequence, three values of diffusion factor b (0, 1000 and 2500 s/mm²) and 60 directions of diffusion gradients for each non-zero b-factor. The following the pulse sequence parameters were chosen for the study: TR=10,000 ms, TE=103.4 ms, FOV=240×240 mm, 80×80 image matrix with subsequent interpolation up to 256×256, 3 mm slice thickness, 0 mm distance between slices, NEX=1, axial scanning plane. The duration of DKI scan was 22 minutes. Additional anatomical images were obtained in the axial plane, consisting of the T2 WI scans (TR=4,300 ms, TE=85 ms, turbo factor of 21, FOV=240×240 mm, 512×512 image matrix, 3 mm slice thickness, 0 mm distance between slices, NEX=2) and T2-FLAIR WI scans (TR=9,500 ms, TE=120 ms, TI=2,250 ms, FOV=240×240 mm, 352×325 image matrix, 5 mm slice thickness, 0 mm distance between slices, NEX=1) registered before intravenous administration of the contrast and T1 WI scans (TR=875 ms, TE=85 ms, FOV=240×240 mm, 384×384 image matrix, 3 mm thickness of slices, 0 mm distance between slices, NEX=2), registered before and after intravenous administration of Gd-containing contrast (at a concentration of 0.1 mmol Gd per 1 kg of a patient’s weight). DKI was performed before the contrast enhancement.

Post-processing of the resulting DKI data set was performed in a number of software packages: MATLAB (MathWorks, USA, http://www.mathworks.com/), FSL (FMRIB Software Library v5.0, Oxford, UK, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [20—22], ExploreDTI (the Netherlands, http://www.exploredti.com/), ITK-Snap (www.itksnap.org) [23], Mango (http://www.nitrc.org/projects/mango). The following quantitative parameters of diffusion kurtosis and diffusion tensor were obtained after the processing: mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), kurtosis anisotropy (KA), mean diffusion (MD), axial diffusion (AD), radial diffusion (RD), fractional anisotropy (FA), relative anisotropy (RA).

The zones of interest (ZOIs) for measuring diffusion parameters in the solid part of the tumor (Fig. 1) and in the zone of the contralateral normal appearing white matter (CNAWM) (Fig. 1c) were selected manually at the maps of mean kurtosis using ITK-SNAP and anatomical MRI data (T1 WI scans before and after contrast enhancement, T2 WI and T2-FLAIR WI scans). The selected ZOIs were automatically transferred to the maps of all other diffusion parameters. Cystic and necrotic tumor components and peritumoral edema of the brain tissue were excluded from the ZOIs.

It is well known that with time most gliomas progress towards the state of higher malignancy and higher proliferative activity [24]. However, many glial tumors have heterogeneous structure, which can simultaneously contain areas with different degrees of malignancy and proliferative activity. In pathomorphology, the true degree of malignancy and proliferative activity of a tumor are defined as the highest values for a part of the tumor. Therefore, in our study the ZOIs included only parts of the tumor with the highest MK values (Fig. 1), which, in our opinion, corresponded to the most malignant parts of the tumor, and, hence, those with the highest proliferative activity [25]. The ZOIs did not include tumor infiltration zones containing brain tissue, which could have 2500 s/mm² pulse sequence, three values of diffusion factor b (0, 1000 and 2500 s/mm²) and 60 directions of diffusion gradients for each non-zero b-factor. The following the pulse sequence parameters were chosen for the study: TR=10,000 ms, TE=103.4 ms, FOV=240×240 mm, 80×80 image matrix with subsequent interpolation up to 256×256, 3 mm slice thickness, 0 mm distance between slices, NEX=1, axial scanning plane. The duration of DKI scan was 22 minutes. Additional anatomical images were obtained in the axial plane, consisting of the T2 WI scans (TR=4,300 ms, TE=85 ms, turbo factor of 21, FOV=240×240 mm, 512×512 image matrix, 3 mm slice thickness, 0 mm distance between slices, NEX=2) and T2-FLAIR WI scans (TR=9,500 ms, TE=120 ms, TI=2,250 ms, FOV=240×240 mm, 352×325 image matrix, 5 mm slice thickness, 0 mm distance between slices, NEX=1) registered before intravenous administration of the contrast and T1 WI scans (TR=875 ms, TE=85 ms, FOV=240×240 mm, 384×384 image matrix, 3 mm thickness of slices, 0 mm distance between slices, NEX=2), registered before and after intravenous administration of Gd-containing contrast (at a concentration of 0.1 mmol Gd per 1 kg of a patient’s weight). DKI was performed before the contrast enhancement.

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increased values for kurtosis and anisotropy and reduced those for diffusion (Fig. 2).

Kurtosis and tensor parameters of the tissues and structures of the brain vary based on localization of the tumor, age and gender of the patient [26—30]. Since diffuse gliomas are characterized by diffuse infiltrative growth in the brain matter, their diffusion parameters may depend on diffusion properties of the brain tissues. In order to compensate for the aforementioned individual features, we have calculated normalized tumor diffusion parameters based on the corresponding parameters of the CNAWM, using the following formula: normalized MK = MKtumor/MKCNAWM, and so on for each parameter (Fig. 1c).

The following goals have been achieved during the study.

1. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and their absolute and normalized diffusion parameters.
2. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and diffusion parameters of the CNAWM.
3. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and their degree of malignancy.
4. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and accumulation of the contrast.
5. Investigation of the correlation between gliomas degree of malignancy and accumulation of the contrast.

Spearman correlation coefficients were used in all cases, and the threshold of statistical significance was set at $p < 0.05$.

According to generally accepted mathematical standards, a correlation was considered to be very weak for $0 < r < 0.2$, weak for $0.2 < r < 0.5$, average for $0.5 < r < 0.7$, strong for $0.7 < r < 0.9$, and very strong for $0.9 < r < 1$.

**Results**

The correlations between the gliomas proliferative activity index (Ki-67/MIB-1 LI) and their diffusion parameters are presented in Table 1. The correlation between the glioma proliferative activity index (Ki-67/MIB-1 LI) and all absolute and normalized diffusion parameters, except for absolute values of FA and RA, was found to be statistically significant and reliable ($p < 0.05$). Kurtosis (MK, AK, and RK) and anisotropy (KA, FA, RA) values increased, and diffusivity (MD, AD, RD) values decreased with the increase in the glioma proliferative activity index. The proliferative activity index was strongly correlated with absolute RK ($r = 0.71; p = 0.000001$) and normalized MK ($r = 0.8; p = 0.000001$), AK ($r = 0.71; p = 0.000001$), RK ($r = 0.81; p = 0.000001$) and RD ($r = 0.71; p = 0.000001$). Normalized values of RK and MK displayed the strongest correlation with gliomas Ki-67/MIB-1 LI values (Fig. 3).

The correlations between the gliomas proliferative activity index (Ki-67/MIB-1 LI) and the CNAWM diffusion parameters are shown in Table 2. Statistically significant weak correlation was observed for RK ($r = 0.36; p = 0.014$), KA ($r = 0.39; p = 0.007$), RD ($r = 0.35; p = 0.017$), FA ($r = 0.42; p = 0.003$), and RA ($r = 0.41; p = 0.004$) values of the contralateral white matter of the brain.

The analysis performed in our study confirmed an opinion expressed by other authors that the standard MRI with intravenous contrast has only limited capabilities in diagnostics of gliomas degree of malignancy and proliferative activity. According to our data (Table 3), there is a weak positive correlation between gliomas Ki-67/MIB-1 LI values and contrast enhancement ($r = 0.37; p = 0.0148$) and an average positive correlation between gliomas histological grade and contrast enhancement ($r = 0.5; p = 0.0001$), whereas the correlation between gliomas Ki-67/MIB-1 LI values and degree of malignancy is very strong ($r = 0.91; p = 0.0001$).

**Discussion**

Nowadays, diffusion-weighted imaging and DTI are widely used in preoperative diagnosis of glial neoplasms [7, 11—17, 28, 31—45]. The technique allows the characterization of isotropic and anisotropic diffusion, based on the assumption that molecular diffusion in the brain tissue has Gaussian distribution. However, the presence of a large number of microstructural units in the brain tissues (cells, cell membranes and organelles, multidirectional nerve processes, extracellular and intracellular liquids, membrane ion pump, etc.) complicates and hinders molecular diffusion, which is, in fact, non-Gaussian in nature. DKI has been successfully used to describe the non-Gaussian diffusion, allowing simultaneous assessment of both Gaussian and non-Gaussian components of molecular diffusion [46, 47]. DKI provides neuroradiologists with a whole arsenal of quantitative parameters that characterizes the microstructure of the brain: diffusion tensor parameters (MD, AD, RD, FA, RA), which can also be obtained with DTI, and diffusion kurtosis parameters (MK, AK, RK, KA) [30, 47].

A number of papers dedicated to the study of correlations between DTI parameters, namely MD and FA, and Ki-67/MIB-1 LI values have been published [7, 11—19]. A statistically significant negative correlation have been established between MD and Ki-67/MIB-1 LI [11, 13—15, 19], and a statistically significant positive one between FA and Ki-67/MIB-1 LI of gliomas [11, 13—16]. Other studies had revealed a statistically significant negative correlation between the minimal MD and Ki-67/MIB-1 LI values of gliomas [12, 18]. These works do not contradict our results. Yet, the literature data on correlations between the glial tumors proliferative activity index and DTI parameters are contradictory. Some authors [17] have come to the opposite conclusion, arguing that FA is negatively correlated and MD is positively correlated with gliomas Ki-67/MIB-1 LI values. Another study [7] failed to found statistically significant correlation between DTI parameters and Ki-67/MIB-1 LI values for glioblastomas.

A particular feature of our work was the investigation of a correlation between the proliferative activity index and diffusion parameters in the most malignant parts of glial tumors. Diffusion parameters were measured only in the solid parts of the tumors with maximum values of MK [25], and not in the entire volume of gliomas. Necrosis and cystic components of gliomas, peritumoral edema, and parts of the tumor containing the remnants of the brain tissue were excluded from the zones of measurement. Necrosis and cystic components of gliomas have low
values of kurtosis (MK, AK, RK) and anisotropy (KA, FA, RA), and high values of diffusion (MD, AD, RD) since their molecular diffusion is close to isotropic Gaussian in nature. The values of kurtosis, diffusion and anisotropy in peritumoral edema of the brain tissue and tumor areas, containing the residual white matter, differ from those in the central part of gliomas due to the presence of the nerve fibers residues [14, 25, 48].

Table 1 shows that all absolute and normalized diffusion parameters, except for absolute RA and FA, are statistically significantly correlated with Ki-67/MIB-1 LI. Higher Ki-67/MIB-1 LI values of gliomas imply more active division of the tumor cells and more rapid growth of the tumor, which lead to increased cell density in the tumor and reduction in the extracellular space. These factors complicate and limit the diffusion of water molecules in the tumor, and, in our opinion, are the

Fig. 1. Anaplastic astrocytoma of the left frontal lobe.
a — diffusion parameters.

Fig. 1 is continued on the next page
main reasons for the increase in kurtosis parameters (MK, AK, RK) and reduction in diffusion parameters (MD, AD, RD) with the increase in Ki-67/MIB-1 LI values. The reduction of intercellular space is also an important cause of statistically significant increase in

anisotropy (absolute KA, normalized KA, FA, RA) with an increase in glial tumors Ki-67/MIB-1 LI values. Since glial tumors have neuroepithelial genesis and tend to exhibit diffuse and infiltrative growth into the brain tissue, the individual characteristics of patients (tumor localization, age, gender, etc.) may affect the diffusion parameters of the tumor. Therefore, we have performed normalization of gliomas diffusion parameters to the contralateral normal appearing white matter. Normalized MK ($r=0.8; p=0.000001$) and RK ($r=0.81; p=0.000001$) exhibited the strongest correlation with gliomas Ki-67/MIB-1 LI, which confirms the relevance of normalization. Diffusion kurtosis parameters showed better correlation with the proliferative activity index compared with diffusion tensor parameters. It can be attributed to the fact that kurtosis describes the non-Gaussian molecular diffusion typical for biological tissues.

There are some articles showing a statistically significant relationship between DKI parameters and gliomas degree of malignancy (WHO Grade), which report an increase in diffusion kurtosis parameters and anisotropy and decrease in diffusion tensor parameters with the increasing degree of malignancy [25, 49, 50]. Similar dynamics of diffusion parameters was observed in case of increase in the gliomas proliferative activity (see Table 1), which corresponds to a very strong correlation between the proliferative activity and degree of malignancy (see Table 3). The gliomas proliferative activity is one of the main factors determining their degree of malignancy (WHO Grade) and it affects the

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**Fig. 1. Anaplastic astrocytoma of the left frontal lobe. Continued.**

b — T2 WI; c — ZOs around the tumor and the contralateral normal appearing white matter at the MK maps. The zone of interest includes the parts of the tumor with maximum MK values, which corresponds to the maximum malignancy and proliferative activity.

**Fig. 2. Diffuse grade II astrocytoma, T2 WI.**

Arrows indicate the parts of the tumor containing residual brain tissue.
Table 1. Correlation between Ki-67/MIB-1 LI values and diffusion parameters of the tumor

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Spearman correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67/MIB-1 LI &amp; CK</td>
<td>0.69</td>
<td>0.000001</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; AK</td>
<td>0.68</td>
<td>0.000001</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; RK</td>
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<td>0.000001</td>
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<tr>
<td>Ki-67/MIB-1 LI &amp; KA</td>
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<td>Ki-67/MIB-1 LI &amp; MD</td>
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<tr>
<td>Ki-67/MIB-1 LI &amp; RD</td>
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<td>0.158110</td>
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<td>Ki-67/MIB-1 LI &amp; norm RA</td>
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Table 2. Correlation between Ki-67/MIB-1 LI values and diffusion parameters of the CNAWM

<table>
<thead>
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<th>Indicator</th>
<th>Spearman correlation coefficient</th>
<th>p-value</th>
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</thead>
<tbody>
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<td>Ki-67/MIB-1 LI &amp; CK</td>
<td>−0.17</td>
<td>0.242</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; AK</td>
<td>0.15</td>
<td>0.302</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; RK</td>
<td>−0.36</td>
<td>0.014</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; KA</td>
<td>−0.39</td>
<td>0.007</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; MD</td>
<td>0.22</td>
<td>0.125</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; AD</td>
<td>−0.17</td>
<td>0.245</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; RD</td>
<td>0.35</td>
<td>0.017</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; FA</td>
<td>−0.42</td>
<td>0.003</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; RA</td>
<td>−0.41</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Fig. 3. Glioblastomas with different Ki-67/MIB-1 LI values.
The increase in Ki-67/MIB-1 LI is accompanied by the marked increase in the tumors MK values, whereas all tumors have the same characteristics on T1 WI, nonuniform accumulation of contrast medium, a zone of necrosis, etc.
values of the tumor diffusion parameters. Investigation of relationships between other factors that define gliomas degree of malignancy and DKI parameters is also of great scientific interest and could be a subject of further research.

Table 2 shows that gliomas Ki-67/MIB-1 LI is statistically significantly correlated with some diffusion parameters of the contralateral normal appearing white matter. Several authors [51, 52] believe that diffuse glial tumors are systemic diseases of the central nervous system rather than local tumor processes. They have demonstrated the presence of the tumor cells in different brain structures, which were unaltered according to standard MRI, at a considerable distance from the glioma [52]. Statistically insignificant trend towards increase in AK and reduction in AD of the CNAWM with the increase in Ki-67/MIB-1 LI may reflect the increase in proliferation of glia or tumor cells and increase in the density of glial or tumor cells in the CNAWM as proliferative activity of the primary tumor intensifies. A significant reduction in RK ($r=-0.36$; $p=0.014$) and significant increase in RD ($r=0.35$; $p=0.017$) of the CNAWM with the increase in tumor Ki-67/MIB-1 LI may reflect the destruction of nerve fibers by tumor cells, which becomes more pronounced with increase in the glioma proliferative activity (since the average age of HGG and LGG patients is not significantly different (Table 4), the observed changes in RK and RD of the CNAWM cannot be attributed to development of atrophic changes in nerve fibers due to more advanced age of the patients). Statistically significant reduction in KA ($r=-0.39$; $p=0.007$), FA ($r=-0.42$; $p=0.003$) and RA ($r=-0.41$; $p=0.004$) values of the CNAWM with the increase in gliomas Ki-67/MIB-1 LI may be caused by both the destruction of the nerve fibers in the contralateral white matter and increased proliferation of tumor or glial cells.

One disadvantage of our study may be the fact that the ZOIs in gliomas were selected in the parts with the highest MK values, however it was not always known which exact portion of the tumor was subjected to pathomorphological and immunohistochemical examination. In future studies, higher number of patients will allow investigation of the relationship between DKI parameters and Ki-67/MIB-1 LI values within a group of patients with gliomas of one particular degree of malignancy (to exclude the influence of other factors, which constitute the degree of malignancy, on the diffusion parameters values, e.g. vascularization, nuclear atypia, number of mitoses, micronecrosis etc.) and with a specific histological subtype of gliomas (e.g., diffuse fibrillary astrocytomas or oligodendrogliomas), which will increase the validity of the results.

**Table 3.** Correlation between Ki-67/MIB-1 LI values, grade of the tumor (WHO Grade) and accumulation of the contrast

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Spearman correlation coefficient</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67/MIB-1 LI &amp; WHO Grade</td>
<td>0.91</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ki-67/MIB-1 LI &amp; accumulation of contrast agent</td>
<td>0.37</td>
<td>0.0148</td>
</tr>
<tr>
<td>WHO Grade &amp; accumulation of contrast agent</td>
<td>0.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 4.** Age characteristics of the patients with high and low grade gliomas

<table>
<thead>
<tr>
<th>Indicator</th>
<th>LGG</th>
<th>HGG</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Patients age (Mean±SD), years</td>
<td>37.7±9.6</td>
<td>43.8±14.7</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

**Conclusion**

DKI parameters are significantly strongly correlated with the gliomas proliferative activity index. A statistically significant correlation has been observed between the gliomas proliferative activity and DKI parameters of the contralateral normal appearing white matter. DKI demonstrated high sensitivity in detection of microstructural changes that occur with increasing malignancy of gliomas both in the tumor and in the unaltered, according to standard MRI, brain structures.

Authors declare no conflict of interest.
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The research conducted by the authors and the results presented in the article have great scientific novelty and are extremely relevant. The authors used a novel diagnostic technique, diffusion kurtosis imaging, which has a number of advantages over the diffusion tensor MRI and allow determination of not only the flow rate of molecular diffusion, but also, importantly, quantification of the resistance to molecular diffusion in different directions. The work is original, because the authors were the first ones to use diffusion kurtosis imaging in the diagnosis of gliomas degree of malignancy based on the Ki-67/MIB-1 labeling index of glial brain tumors. Neuroimaging, pathological and immunohistochemical correlations are described in detail and their basics are analyzed for brain gliomas with different degrees of malignancy and the use of DKI.

The obvious novelty of this work is the identification of structural changes that the authors observed in the contralateral hemisphere of the brain with an increase in Ki-67/MIB-1 labeling index of the glial brain tumors. The authors suggest that changes in the contralateral hemisphere may be due to increased proliferation of the glia in patients with high values of Ki-67/MIB-1 LI of the glial tumor in contrast to patients with lower values of Ki-67/MIB-1 LI of the tumor. The authors believe that these data support the hypothesis that glial tumors are diseases of the entire brain, rather than local tumor pathological processes.

Clinical and radiographic studies convincingly demonstrate high efficiency of DKI in the diagnosis of degree of brain gliomas malignancies; the new method of neuroimaging undoubtedly has great diagnostic potential. The fundamental provisions elucidated by the authors are objectively supported by the presented material, have fundamental innovative value and represent the basis for further research on the objectification of diagnostic of glial tumors degree of malignancy during preoperative stage.

V.L. Puchkov (Moscow, Russia)


Awake Craniotomy: Analysis of Complicated Cases

A.S. KULIKOV, G.L. KOBYAKOV, A.G. GAVRILOV, A.YU. LUBNIN

Burdenko Neurosurgical Institute, Moscow, Russia

Awake craniotomy is recognized as a method that can reduce the frequency of neurological complications after surgery for gliomas located near the eloquent brain regions. Unfortunately, even the use of this technique cannot ensure good neurological outcome. This paper discusses the reasons of these complications and possible prevention methods. Material and methods. A total of 162 awake craniotomies were performed in our clinic. Results. 152 patients were discharged from the clinic with good outcomes. In 10 (6%) cases, there was sustained severe neurological deficit. These complications were associated with anatomic or ischemic injury of subcortical pathways and internal capsule. Conclusion. Awake craniotomy is an effective tool for brain language mapping and prevention of neurological deterioration. Severe neurological complications of awake craniotomy are associated with underestimated neurosurgical risks, especially in terms of blood vessel injury and resection depth. Meticulous planning of the surgery and adequate use of mapping facilities are the main ways of prevention of these complications.

Keywords: awake craniotomy, brain mapping, complications, gliomas.

The problem of iatrogenic injury of the most functionally important parts of the brain is a pressing issue virtually since the creation of neurosurgery as a separate medical specialty. Resection of the space-occupying lesions of the brain is inevitably associated with the risk of damage to the surrounding intact tissues.

Tumors, especially glial ones, are characterized by wide variety of possible locations in the tissue of the cerebral hemispheres, therefore they can occur either in the areas with lower functional importance of neurons or in the areas with high concentration of cells whose dysfunction leads to apparent disability of a patient. According to classical neurology, the latter refers to the areas of precentral and postcentral gyri responsible for motor and sensory function, as well as postero-inferior portions of the frontal lobe and postero-superior portions of the temporal lobe involved in speech functions. Location of lesions in these regions usually attracts the most attention of neurosurgeons when planning surgery on the cerebral hemispheres.

Modern neurophysiological methods (assessment of motor evoked potentials, transcranial stimulation, etc.) enable quite reliable intraoperative identification (of course, without the use of muscle relaxants) of the location of motor areas of the cortex and corticospinal motor pathways under conventional general anesthesia. However, mapping of language areas and associated pathways requires intraoperative awakening of the patient in order to perform specific tests, i.e. the surgery should be conducted according to “awake craniotomy” method.

It would seem that the implementation of these capabilities can ensure the protection of functionally important areas of the brain during the resection of space-occupying lesions. However, the experience gained during awake craniotomies at our clinic shows that this thesis does not fully represent the facts.

In this paper, we tried to analyze the causes and possible methods of prevention of sustained neurological disorders arising during operation or in the early postoperative period in patients who underwent surgical intervention with intraoperative mapping of language areas of the brain according to awake craniotomy protocol.

Material and methods

During the period from 1996 to 2014, a total of 162 operations for resection of space-occupying lesions of the brain with intraoperative mapping of language areas of the brain were performed at the Burdenko Neurosurgical Institute. Of these, arteriovenous malformations (AVMs) were resected in 4 (2%) cases, foci of focal cortical dysplasia with underlying pharmaco-resistant epilepsy were resected in 9 (6%) cases, and tumors, especially gliomas characterized by varying degrees of malignancy and located in the dominant hemisphere were resected in the remaining 149 (92%) cases.

Indications to the surgery with intraoperative mapping of the language areas included location of a lesion near the conventional anatomical boundaries of Broca’s and Wernicke's areas (i.e. postero-inferior portion of the frontal lobe and postero-superior portion of the temporal lobe) according to MRI, as well as sufficient speech functions to perform test tasks at admission. Since 2010, the results of functional MRI with mapping of language areas were also widely used to determine surgical indications. Surgical treatment (operation with intraoperative awakening and electrophysiological mapping of language areas of the dominant hemisphere) was carried out according to the procedure developed at the Burdenko Neurosurgical Institute and reported in our previous works [1—5].
Results

Among the patients who underwent awaked craniotomy, 152 (94%) individuals have been discharged from the hospital with a positive outcome (improvement or the absence of worsening of neurological status). However, there was an apparent increase in neurological deficit in 10 (6%) patients, and therefore these treatment outcomes were determined as worsening at discharge (Table 1). It should be noted that none of treated patients had pronounced neurological deficit at the first-time admission. Only some patients had mild right-sided hemiparesis and slight speech disorders (which did not hampered execution of tasks for speech function testing).

In the postoperative period, all these patients had severe motor aphasia. It was combined with deep hemiparesis up to and including plegia in 6 cases, deep paresis, mainly in the hand in 2 cases and in the leg in 1 case. In 3 cases, anatomical injury of the cortical (1 case) and subcortical (2 cases) structures are the most probable causes of these disorders, especially the invasion of the internal capsule (Fig. 1). In 5 cases, the unfavorable outcome was likely to be associated with damage to the blood vessels and ischemia of the internal capsule (Fig. 2, 3).

In one case, the deterioration at discharge was associated with progression of the preoperative symptoms after partial resection of the tumor tissue and subsequent edema. Another case of poor neurological outcome was observed in the patient with postoperative hematoma in the immediate postoperative period, which necessitated revision of the surgical wound.

Discussion

Currently, world literature provides quite a lot of publications, reporting the series of resections of disseminated brain tumors with intraoperative mapping of language areas [6—10]. The present article reports the series of case studies performed in our clinic, which is rather large according to international standards and can be included to the aforementioned series. Most professionals, who regularly use awake craniotomy in clinical practice, recognize this approach as a method that can significantly improve treatment outcomes in patients with space-occupying lesions of the brain. According to most researchers, this approach reduces the risk of iatrogenic damage to functionally important areas of the brain (eloquent areas) [7, 11, 12]. Radicality of tumor resection is an equally important aspect of treatment for both benign and malignant gliomas. Its prognostic importance has been proved in numerous studies [13—16]. In this context, the possibility of more confident navigation in the surgical wound, i.e. reasoned efforts towards radical resection, can be considered as another advantage of intraoperative mapping of the language areas of the brain [8, 10].

Of course, within the context of this discussion we can not neglect the fact that there is also skepticism about the influence of the awake craniotomy method on the quality of treatment of patients with gliomas in the literature. In particular, in the study by D. Gupta et al. [6], which was a randomized prospective study including 53 operations, neurological deficit increased in 23% of patients in the awake craniotomy group compared to 15% in the general anesthesia group. At the same time, more radical tumor resection was observed in the 2nd group. No significant differences had been found between these groups. On the other hand, more extensive studies, such as large-scale meta-analysis by De W. Hammer et al. [17], which included 90 studies involving a total of more than 8,000 patients, showed that intraoperative mapping lead to more than twofold better results in terms of the frequency of the newly established post-operative

<table>
<thead>
<tr>
<th>No</th>
<th>Clinical manifestations</th>
<th>Reason</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hemiplegia, motor aphasia</td>
<td>Damage to the fibers of the internal capsule</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Severe hemiparesis, aphasia</td>
<td>Acute hematoma in the tumor bed, damage to pathways</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe hemiparesis of the hand, aphasia</td>
<td>Ischemia of the internal capsule pathways</td>
<td>Recovery of speech in six months. Residual hemiparesis of the hand</td>
</tr>
<tr>
<td>4</td>
<td>Motor aphasia, hemiparesis, mainly in the foot</td>
<td>Mechanical damage to pathways</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Aphasia and hemiparesis</td>
<td>Small volume of resection</td>
<td>Deterioration with underlying edema after partial resection of the tumor</td>
</tr>
<tr>
<td>6</td>
<td>Hemiplegia, aphasia</td>
<td>Ischemia of the internal capsule pathways</td>
<td>Significant regression within 1 month</td>
</tr>
<tr>
<td>7</td>
<td>Aphasia</td>
<td>Ischemia of the internal capsule pathways</td>
<td>Significant regression within 1 month</td>
</tr>
<tr>
<td>8</td>
<td>Plegia of the hand, paresis of the foot, motor aphasia</td>
<td>Ischemia of the internal capsule pathways</td>
<td>Significant regression within 1 month</td>
</tr>
<tr>
<td>9</td>
<td>Aphasia, severe hemiparesis</td>
<td>Damage to cortical centers (hand) and pathways</td>
<td>Absence of movements in the hand during resection. Aphasia manifested in the postoperative period</td>
</tr>
<tr>
<td>10</td>
<td>Aphasia, severe hemiparesis</td>
<td>Ischemia of the internal capsule pathways</td>
<td></td>
</tr>
</tbody>
</table>
neurological deficits (3.4% versus 8.2% in the group without mapping; \( p < 0.05 \)), as well as the frequency of complete resection (75% vs 58% in the group without mapping; \( p > 0.05 \)).

Our experience confirms the advantages of the method of intraoperative mapping of language areas. Favorable surgical outcomes (according to neurological status) in 94% of patients in the given group of high-risk patients can be safely regarded as proof of advisability of clinical application of awake craniotomy technique.

Interestingly, in the first operations with awakening in our series, there were mainly intraoperative complications such as seizures and brain edema, but the incidence of severe neurological deficit was low [1, 18]. This is probably due to some reasonable caution in tumor resection (possibly due to its radicality) when mastering the method.

However, a large-scale practical application of awake craniotomy unfortunately showed that successful mapping of the cortical language areas does not always guarantee the safety of motor and speech functions of the nervous system, since it does not protect against damage to the subcortical structures. Maintaining patient’s consciousness when removing a tumor, which enables continuous neurological monitoring of the patient, does not always protect against unintended iatrogenic damage.

Fig. 1. Preoperative and postoperative MRI of patient No 1 (expansion of resection area to the projection of the internal capsule can be observed).

Fig. 2. Preoperative and postoperative MRI of patient No 8 (right — ischemic foci near the internal capsule).
It should be noted that these complications occurred in patients during about 15 years of our experience of these operations. Therefore, the awakening technique currently differ from that in “early” patients: in the past years, anesthesia was induced after cortex mapping and the surgery for tumor resection proceeded without the contact with the patient (for this reason, neurological deficit in some our patients was caused by direct damage to conduction paths). Currently, we are committed to contacting the patient during surgery (if the patient can psychologically withstand this approach). During the resection, the patient is requested to move limbs, repeat counting, etc., while we repeat mapping of the brain and association paths from time to time. The experience of these operations in our clinic shows that it is possible to stop resection of the tumor and perifocal zone at the moment of slightest increase in neurological deficit in a significant proportion of patients. It is also possible that the feeling of controllability of the process of abnormal tissue resection and the desire to achieve maximum allowed cytoreduction, which is preconditioned by awake craniotomy, in some cases, can lead to an unjustified extension of the resection zone into the depths of the wound, where the risk of damage is the highest.

On the other hand, the aforementioned severe complications undoubtedly cannot be considered specific to awake craniotomy. They are partially due to the shortcomings of surgical tactics and techniques, i.e. failure to maintain the balance between anatomical capability and physiological permissibility, which are the cornerstones of any surgical intervention regardless of anesthetic conditions of the surgery.

In this regard, it seems advisable to discuss possible ways to prevent severe neurological complications from the standpoint of the aforementioned features of the surgery of hemispheric diffuse tumors.

Unfortunately, the issue of surgical complications of awake craniotomy is poorly covered in the literature. Some authors [19, 20] rather discuss the comparative decrease in the incidence of neurological deficit in the groups of patients where the mapping was successful and functional areas were clearly localized. In particular, N. Sanai et al. [20] report the increase in refractory speech disorders after surgery in 4 (1.6%) of 243 patients who underwent surgery with brain mapping. In all these patients, language areas were not verified according to electrostimulation data. Some other studies demonstrate similar incidence of deterioration in the cases there the areas were not identified during mapping [10, 21]. The authors of these studies suggest that the data on the absence of identified language areas within the trepanation area and the potential benefits of the expansion of trepanation should be interpreted with care for reliable mapping in doubtful cases.

As for the general principles of surgical tactics in resection of diffuse gliomas invading the deep portions of the hemisphere and involving the insula, the data collected by M. Berger et al. [20, 22, 23] at the University of California in San Francisco are quite interesting. Their experience suggests a greater frequency of neurological complications in this group of patients in cases of transsylvian approach to the tumor. For this reason, the authors prefer the transcortical approach. This recommendation is based mainly on the substantially lower risk of damage to the vessels. In the context of the

![Preoperative and postoperative MRI of patient No 10 (large ischemic area near the posterior genu of the internal capsule).](image)
implementation of the awake craniotomy method, we
can also say that manipulations with vessels are often
painful, which greatly complicates the process of
continuous neurological monitoring and mapping of the
subcortical structures during tumor resection. As for the
prevention of damage to blood vessels, the
recommendation to limit the use of diathermocoagulation
and prevent damage to the pia mater during the procedure
seems to be important [24].

We should also keep in mind the anatomical studies
of the pathways of the brain in general, and fronto-
temporal region in particular, which provide the
connection between speech centers in the dominant
hemisphere [25]. Injury of these pathways in various
areas (depending on the direction of tumor growth and
therefore surgical manipulations) can lead to various
speech disorders and motor loss. In our observations
(patients No 1 and 4), there was the injury of a large
group of fibers of the internal capsule according to the
postoperative imaging, which manifested as severe
increase in neurological deficit in the form of hemiplegia,
hemianesthesia, and pronounced sensorimotor aphasia.
When planning the surgery, one should keep in mind the
peculiarities of the anatomical structure of the associative
fibers involved in the functioning of the speech centers,
since the resolution of MR tractography is currently very
high [26—30]. Therefore, careful preoperative planning
using MR tractography will reduce the risk of
intraoperative events.

The anatomical classification of the location of
insular gliomas suggested by N. Sanai and M. Berger [23]
is quite interesting from a prognostic viewpoint. The
authors state that tumors located mostly anteriolad of the
“horizontal line” through the foramen of Monro (axial
projection) may be subjected to larger volume of
resection. Tumor growth in the areas located posteriolad of
this imaginary line (axial projection) is associated with
greater risk of dysfunctions (due to the proximity of the
tumor infiltration to the Rolandic fissure and posterior
limb of the internal capsule), i.e. manipulations in these
areas require the most careful handling of tissues even
during awake craniotomy.

An important role in preventing neurological
problems undoubtedly belongs to preservation of
lenticulostriate arteries supplying the internal capsule
and full utilization of intraoperative electrophysiological
mapping of pathways to limit the medial margin of tumor
resection in order to preserve the fibers of the corticospinal
tract [22, 31, 32].

Conclusion
Awake craniotomy is rightly recognized as the
method that significantly reduces the incidence of
worsening of neurological disorders in the postoperative
period after removal of tumors adjacent to the eloquent
areas of the brain. The more is the pity, when the use of
this techniques, which is difficult to implement and
requires the involvement of the team of highly qualified
specialists, nevertheless results in adverse neurological
outcome. Our experience shows that these cases are most
commonly associated with underestimated neurosurgical
risk, especially the risk of ischemic damage, insufficient
use of the potential of pathway mapping, preoperative
planning, and modern neuroimaging tools, in
particular MR tractography. These problems should be
solved using careful, accurate planning of the intervention
and mapping of the structures based on the evaluation of
the conventional and specific risks of manipulations, as
well as the serious training of specialists to use this
technique in centers with sufficient clinical experience.

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Authors declare no conflict of interest.

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routine surgical approach to treating patients with supratentorial intraxial
The term “Awake craniotomy” was proposed in 1959 by De Castro and Mundeleer as a method to optimize the neurosurgery of the pharmacoresistant forms of epilepsy. The experience in application of this method of anesthesia in neurosurgical interventions requiring localization of high cortical functions by their intraoperative activation, in particular speech, was accumulated over the last years. The authors of this article have the world’s greatest experience of these interventions, which enabled them to carry out thorough analysis of failures resulting in postoperative neurological deficit, both their own and reported by other researchers. Since the reviewer is out of practice in this problem, his opinion is reduced to the level of methodological comments.

In this regard, the authors’ approach is worthy of respect as it provides analysis performed cooperatively by neurosurgeons and neuroanaesthesiologists. The results of application of this technique are obviously successful, since the deterioration of neurological status was observed only in 6% of patients. When analyzing the causes of complications, they should be divided into avoidable and unavoidable ones. From this viewpoint, the authors reached the limit of safety of anesthetic care, since all problems significant for deterioration of neurological status, such as seizures, nausea, vomiting, and hemodynamic crises, were eliminated under the conditions of routine neurosurgery. Neurosurgeons suggest options to improve the technique by optimizing the approach, but it is the matter of discussion for experts. We suggest that the phrase “...failure to maintain the balance between anatomical viability and physiological permissibility is the cornerstone of any surgical intervention regardless of anesthetic conditions of the surgery” comprehensively defines the problem of interdisciplinary cooperation between neuroanaesthesiologists and neurosurgeons. In fact, the natural desire to achieve optimal coreduction, underpinned by the sense of safety due to the direct contact with the patient, brings the operator to the “yellow sector”, where the tissue injury results in a deficit after a while, by the time of awakening. All methods used for preoperative correction of the allowed area of neurosurgical activity (navigation mapping, functional MRI, and tractography) provide maximum possible assessment of correlation between the anatomy and functions. Of course, their complex application is appropriate and, along with improvement of neurosurgical approaches, will result in prevention of some complications. However, the following problems still remain out of control: the effects of perfusion-metabolic mismatch, local inflammatory response, and functional remodeling. These processes are the natural physiologically and genetically determined response to any exogenous impact and result in unavoidable complications in

Commentary

some patients. Our knowledge and counteraction methods are still insufficient to prevent these complications.

The article was written at the highest methodological level, provides the comprehensive picture of the problem, and its publication will be a worthy acquisition for a specialized journal.

A.A. Belkin (Ekaterinburg, Russia)
Intramedullary spinal cord tumors (IMSCTs) occur both in children and adults and are a rare pathology. Our experience shows that tumor characteristics may vary depending on patients’ age. Very few studies in the available literature focus on comparative analysis of this type of neoplasms in different age groups. **Objective.** To perform comparative analysis of the main epidemiological characteristics of intramedullary tumors in children and adults using a large surgical series and to identify possible differences. **Material and Methods.** Prospectively collected data about the nature and the main characteristics of intramedullary tumors in 224 pediatric (up to 18 years old inclusive) and 242 adult patients were used for this study, a total of 507 cases of resection of intramedullary tumors. **Results.** Pediatric IMSCTs are more extensive; at admission children are in the worse clinical condition compared to adults. The astrocytoma/ependymoma ratio was 83/17 in children and 21/79 in adults. There were age-related differences in tumor localization. Hence, adults predominantly had tumors of the cervical spine, while children typically had tumors of the thoracic spine and holocord tumors. Conclusions. The revealed differences in epidemiological and clinical characteristics of intramedullary tumors in children and adults have confirmed the fact that diffuse tumors predominate among pediatric patients and specified the astrocytoma/ependymoma ratio in different age groups. The analysis of the size and clinical presentation of intramedullary tumors in children attests to late diagnosis in this age group. **Keywords:** epidemiology, intramedullary tumors, adults, children.

Intramedullary spinal cord tumors (IMSCTs) belong to the group of rare diseases [1—3]. It is extremely difficult to perform investigations providing the “gold standard” evidence for these cases. In this regard, analysis of personal series will long remain the main source of information on these pathologies. Years of managing IMSCTs patients of different age groups gave the first author a notion of differences between the clinical status in similarly diagnosed children and adults. Some of these differences, including the predominance of astrocytoma in the pediatric subgroup, have already been reported in literature, while others have been not [2—4]. The Medline search did not reveal any studies focusing on comparative analysis of the main epidemiological characteristics of intramedullary tumors in children and adults. The present paper reports the summary statistics on the authors’ surgical experience.

**Material and Methods**

Prospectively collected data on the main epidemiological characteristics of intramedullary tumors
from 224 pediatric (up to 18 years inclusive) and 242 adult patients were analyzed. These data represent 507 surgeries on the removal of IMSCTs performed by one surgeon (YK) primarily at the Burdenko Neurosurgical Institute between 2002 and 2015. It is important to note that all of the patients were histologically diagnosed. Quantitative analysis of the data was performed using the standard methods of descriptive statistics and Wizard and Excel software for Mac OS.

Results

The age distributions of patients with IMSCTs in the pediatric and adult subgroups are presented in Figs. 1 and 2.

Analysis of the diagrams shows that there is a single maximum of incidence of intramedullary tumors in children aged 12—15 years and two maxima in adults aged 30 and 45—50 years.

Functional status at the time of surgery

In practice, children appeared to be in worse clinical condition than adults, which was confirmed by assessing the patients’ functional performance according to the classical McCormick scale [5] and statistical data processing. The analysis showed that a significantly greater number of children are admitted to hospital for surgery when having in the worse functional status corresponding to grades III and IV on the McCormick scale. The revealed difference was statistically significant (Fig. 3).

Fig. 2. Age distribution of IMSCTs in the adult group.

Fig. 3. Distribution of patients over the functional classes of the McCormick classification for children and adults at the time of surgical treatment.
Tumor length expressed as the number of vertebrae

As we have been operating on a significant number of patients with intramedullary tumors, we paid attention to the clear predominance of extensive tumors in children (Fig. 4), which was particularly evident when compared to tumors 1—2 vertebrae long that are typical of the adult group (Fig. 5). In our series, the mean tumor length was 3 segments in adults and 5 segments in children. The difference was statistically significant (Mann-Whitney U-test; \( p<0.001 \)). The correlation analysis revealed a negative dependence between the functional status and tumor length; i.e., patients with more extensive tumors mostly belong to the third and fourth functional groups according to McCormick classification (Fig. 6).

Tumor topography

Topographic classification distinguished cervical (C), cervicothoracic (CTh), thoracic tumors (Th), tumors of the medullary cone (L), and holocord (H) tumors. According to the correlation analysis, adults mostly had tumors with cervical localization (Fig. 7), while children were more likely to have thoracic and holocord tumors (Fig. 8). No age-related differences were detected for cervicothoracic tumor localization. Cervicothoracic tumors were most common tumors affecting the spinal cord segments in both age groups.

Histological types of tumors

The astrocytoma/ependymoma ratio was 83/17 in children and 21/79 in adults. Correlation analysis
provided the possible relation between histological subtypes and the typical age of their clinical manifestation. Thus, ependymoma was typical of the adult group, while all types of astrocytoma (including glioblastoma), epidermoid and anaplastic ependymomas were more common in the pediatric subgroup. The absence of correlation between age and hemangioblastomas (HAB) was unexpected, since HAB initially seemed to occur more frequently in adults. No correlation was found between the age and the incidence rate of malignant tumors (Chi-square test; \( p=0.128 \)).

As repeatedly reported in the literature, the incidence rates of astrocytoma and ependymoma were identical in patients older than 60 years. There were 11 patients of this age in our series, including 8 patients with ependymoma. Metastasis, demyelination, and glioblastoma were revealed for the other three patients. Thus, the astrocytoma/ependymoma ratio in the subgroup of patients older than 60 years was 88/12 (i.e., ependymomas were even more predominant than in the entire adult group).
Discussion

We did not find any available studies focused on comparative characterization of intramedullary spinal cord tumors in children and adults. Our series is unique due to the large number of observations, the almost equal number of patients in both age groups, and the absence of patient preselection. The astrocytoma/ependymoma ratio is the only factor mentioned in the literature as a comparative parameter for pediatric and adult IMSCTs. In most papers devoted to surgery for intramedullary tumors, the reported astrocytoma/ependymoma ratios are 60/40 in adults and 40/30 in children, respectively [3, 6—10]. Our results differ significantly from the previously reported values. The astrocytoma/ependymoma ratio was 83/17 in children and 21/79 in adults.

The prevalence of diffuse and/or poorly circumscribed tumors in children puts additional demands on surgical treatment, including surgeon’s experience and technological support, since the motor-evoked potential monitoring is a critical factor for successful surgical outcome.

We revealed some important, yet previously unreported facts. By the time diagnosis is made, children have the more pronounced neurological deficit, the more extensive tumor and the worse functional status. The reason is not so much the nature of pediatric tumors (there is no evident difference in the ratio between malignant and benign tumors in adults and children) but the lack of attention from parents and physicians to the first non-specific symptoms, such as pain, dysesthesia and scoliosis. That is the only reasonable explanation of the fact that tumors in children are twice as more extensive as in adults by the time of MRI diagnosis and that patients have more pronounced neurological symptoms. The correlation analysis demonstrated an evident correlation between the tumor length and the preoperative functional status. Obviously, late diagnosis is a problem in the pediatric subgroup, since MRI is often postponed until there is the full-scale clinical presentation of spinal cord disorder. Adults have the opposite tendency. Along with the high incidence of age-related spinal cord disorders, wide availability of MRI for their diagnosis provides “incidental” or simultaneous detection of IMSCTs and spondylosis during MRI performed to diagnose intervertebral disc herniation.

Conclusion

The revealed differences in epidemiological and clinical characteristics of pediatric and adult IMSCTs confirmed the prevalence of diffuse tumors in children and specified the astrocytoma/ependymoma ratio in different age groups. The analysis of the length and clinical presentation of intramedullary tumors in children indicates that the primary symptoms are ignored by both parents and physicians, resulting in late tumor diagnosis. The broader use of MRI in diagnosis of children with non-specific spinal symptoms, including pain, scoliosis, and forced head position, will undoubtedly improve the current state-of-the-art in diagnostics and the functional outcomes of surgeries.

Authors declare no conflict of interest.
In this work, the authors analyze their own data on the regularities in formation and clinical manifestation of intramedullary tumors in pediatric and adult groups. It is important to note that combining the adult and pediatric groups seems to be not quite justified due to the features in the clinical course of the intramedullary process and histological specificity inherent to different age groups. At the same time, the largest studies on spinal cavernous angioma (over 600 patients operated on at the same center) consolidated patients aged 2—80 years (J. Badhiwala. J Neurosurg Spine. 2014 Oct;21:4). The authors’ statement about the high evidence level of expert’s opinion is also in contradiction to the generally accepted view, since it is expert’s opinion that lies at the foundation of the evidence pyramid as opposed to the cohort, representative, multicenter and other evidence-based studies that have the highest level of systematic literature reviews (Haynes et al. BMJ. 2006). Of course, the unique experience of the Burdenko Neurosurgical Institute on epidemiology of intramedullary tumors, which are not an orphan disease and have been widely analyzed in literature, requires a comprehensive analysis. Results of these investigations can be comparable to the conclusions drawn by the authors.

The ratio between the histological types of tumors in the pediatric subgroup is quite unconventional. The data of most researchers (A. Menezes et al.) attest to a slight predominance of astrocytic tumors, whereas the authors’ series of pediatric tumors predominantly contains infiltrating tumors. Piloid astrocytoma is traditionally the most common tumor type in pediatric population and is followed far behind by fibrillar astrocytomas. In general, as authors fairly noted, the epidemiology of pediatric tumors reveals some unexpected facts, for example, concerning the significant length of intramedullary tumors in children and the degree of disease manifestation according to the McCormick scale. Taking into account the significant predominance of infiltrating tumors, prognosis of total resection of these tumors, as well as the chances of successful functional outcomes are limited.

As a whole, this work provides a representative analysis of cumulative data with justification of age-related, histopathological, anatomical and morphological proliferation of intramedullary tumors in children and adults. The authors’ conclusions about the reasons of late tumor diagnosis and surgical treatment in pediatric group and the possible ways to overcome this problem are definitely of great interest. Correlation data analysis of tumor length, the functional outcomes of surgical treatment and technical features of the performed operations may probably be used for future research on this subject.

A.O. Gushcha (Moscow, Russia)

REFERENCES

Long-Term Outcomes of SDR in Spastic Cerebral Palsy Patients

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Burdenko Neurosurgical Institute, Moscow, Russia

Aim. Long-term outcomes of selective dorsal rhizotomy (SDR) are not described in detail in the literature. The aim of this study was to systematize and evaluate long-term outcomes of SDR in cerebral palsy (CP) patients from various functional groups. Material and methods. Forty seven patients with spastic CPs were operated on. All patients underwent SDR of the L1—S1 roots under EMG control. In all cases, osteoplastic laminoplasty was used as an approach. Surgical treatment outcomes were evaluated using the Ashworth and GMFM 88 scales. The data were subjected to statistical analysis. The follow-up period ranged from 12 months to 7 years. Results. A significant reduction in spasticity from 4.34±0.53 points before surgery to 1.61±0.45 points after surgery (p<0.001) was observed in most cases. The changes in locomotor functions were maximal in the 3rd GMFM class, increasing from 48±4% points before operation to 52±6% points 12 months after operation (p<0.042). The changes in locomotor functions amounted to 2% in the 4th GMFM class and 1% in the 5th GMFM class. The best functional outcomes were obtained in children under 10 years of age. A positive correlation was found only between the percentage of cut roots and a decrease in spasticity (r=0.85). No correlation between the amount of cut roots and the changes in locomotor functions was observed. No spinal cord deformities were observed in the follow-up period. Conclusion. The degree of spasticity reduction due to SDR is directly dependent on the amount of cut roots. The functional result of SDR is affected not only by a decrease in spasticity but also by the functional status and age of the patient at the time of surgery. In all cases, osteoplastic laminoplasty should be used as an approach to prevent spinal cord deformities.

Keywords: spasticity, cerebral palsy, selective dorsal rhizotomy.

Selective dorsal rhizotomy (SDR) is a neurosurgical procedure performed mainly at the lumbar level for reducing abnormal muscle tone in patients with lower extremity spastic paraparesis. The primary beneficiaries of SDR are children with spastic cerebral palsy (CP) [1, 2]. Spasticity is a stretching velocity-dependent increase in tonic stretch reflexes, resulting from the loss of inhibition of motor neurons by the upper central nervous system structures [3]. Selective dorsal rhizotomy reduces excessive activity by partial cutting of some dorsal spinal roots comprising the myotatic fibers — the pathways terminating the stretch reflex and mediating spasticity [4]. A meta-analysis of short-term outcomes of rhizotomy in three randomized controlled trials was performed in 2002. SDR was shown to lead to a reduction in spasticity, increase in the range of movement, and improvement in motor functions in the short term period (6 months to 1 year) [5—7].

The literature does not describe in detail the long-term outcomes of rhizotomy, being mostly focused on complications, such as spinal deformities and pain. The study of long-term outcomes of rhizotomy since 2011 has led to the following conclusions:

1) the functional result can not be reliably evaluated because changes in the locomotor status are different in various groups (GMFM scale); therefore, the changes in functions should be evaluated separately for each group;
2) the functional outcome should be assessed separately in different age groups;
3) long-term complications of rhizotomy, such as spinal deformities, may not be associated with surgery because they are typical of CP patients in general [8].

A study of SDR outcomes, which was carried out at the Burdenko Neurosurgical Institute in 1996, confirmed a high efficacy of the surgery for reducing abnormal muscle tone in the long-term period [1]. However, the study included a small sample of patients and did not assess the patients using gross motor scales. Complications, such as progressive spinal deformities, were observed in the long-term period, which was probably associated with the use of laminectomy as an approach.

The aim of this study was to systematize and evaluate the long-term outcomes of selective dorsal rhizotomy in CP patients from different functional groups according to the GMFM scale.

Material and Methods

A total of 47 children with CP in the form of lower extremity spastic paraparesis and tetraparesis were studied (Table): 32 (68%) boys and 15 (32%) girls; the mean age was 7.4±6.1 years. All patients before surgery underwent repeated courses of conservative and rehabilitation treatment with a low and unstable clinical effect. Before surgery, all the patients underwent botulinum toxin therapy for lower extremity muscle spasticity (2—6 injections). A clinical effect was absent in 16 patients; 31 patients had a partial clinical effect regressing during subsequent injections. In 5 cases, patients had already undergone orthopedic interventions for fixed contractures: achilloplasty and hamstring tendon lengthening.

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The patients were selected for surgical treatment based on a comprehensive examination with involvement of a neurologist, physiotherapist, orthopedist, and neurosurgeon. The examination protocol included evaluation of muscle tone using the Ashworth’s scale, evaluation of the range of active and passive movements, video recording of gait, and evaluation of the locomotor status based on the Gross Motor Function Measure (GMFM-88) scale. The Ashworth’s scale grades spasticity from 1 to 5, where 1 is normal muscle tone, and 5 is the maximum muscle tone when passive movement is almost impossible. The GMFM scale consists of 88 standard motor function tests. Each test is graded on a four-point scale, depending on a test performance level: 0 — cannot initiate task, 1 — initiates task, 2 — partially completes task, 3 — completes task. The total sum of scores is represented as a percentage. Patients with 20% or less are classified as class 5 (most severe form of cerebral palsy), 20 to 40% as class 4, 40 to 60% as class 3, 60 to 80% as class 2, and 80 to 100% as class 1.

Before surgery, all patients underwent brain MRI to evaluate hydrocephalus and exclude concomitant intracranial pathology as well as MRI of the lumbar spinal cord to identify the medullary cone level. A control examination was carried out 3, 6, and 12 months after surgery and thereafter each year.

Statistical processing of the data was performed using the SPSS Statistics 6.0 software. A correlation analysis using the Pearson correlation coefficient (r) was performed to evaluate the relationship between the amount of cut fascicles and the changes in spasticity and locomotor functions. Given the small sample size and absence of normal distribution in the Kolmogorov-Smirnov test, the Wilcoxon nonparametric test (T) was used to analyze the significant differences between preoperative and postoperative values of muscle tone and locomotor functions in different groups of patients.

The study included patients treated in the period from 2007 to 2014. Patients operated on later were not studied because short-term follow-up interfered with an adequate assessment of the changes in locomotor functions over time. The inclusion criteria were as follows:

1) high muscle tone (3 or more points on the Ashworth scale);
2) conservative therapy failure;
3) botulinum toxin therapy failure.

The contraindications for rhizotomy included:

1) secondary muscular dystonia;
2) hyperkinetic syndrome;
3) somatic contraindications.

Mental retardation was not considered to be a contraindication for rhizotomy.

All patients were operated on under general anesthesia. Before being transported to the operation room, patients were subjected to intramuscular premedication with ketamine and benzodiazepines according to anesthesiologist orders. At admission to the operation room, anesthesia induction, tracheal intubation, and mechanical ventilation were performed. All children underwent placement of a Foley urinary bladder catheter. Anesthesia was maintained with an infusion of propofol and fentanyl under monitoring the depth of anesthesia (BIS monitor). Since the operation was performed under EMG control, it was important to maintain the adequate depth of anesthesia in order to obtain true neurophysiological responses. The use of muscle relaxants was limited to intubation only. Electrodes for intraoperative myography were inserted into the adductor muscles, hamstring muscles, quadriceps and gastrocnemius muscles, and anal sphincter (Fig. 1).

Osteoplastic laminotomy at the T12—L1 level was performed with the medullary cone being in the normal position. In 2 patients with a fixed spinal cord, laminotomy was performed at the L3—L4 level. After opening the dura mater, the medullary cone was identified. The L1 dorsal root was identified in the radicular foramen and was isolated to its branching from the dorsolateral sulcus of the spinal cord. Further, moving along the dorsolateral sulcus downward, the L2—S1 dorsal roots were successively isolated. Each root was divided into several root fascicles. The root fascicles were subjected to intraoperative electrostimulation using a mono- or bipolar stimulator (frequency of 5 Hz, pulse duration of 0.1—0.2 ms, amplitude of 0.5—2 mA). In this case, motor responses in the legs were evaluated. Responses occurring in different muscle groups or on the contralateral side were considered as abnormal. The fascicles producing these responses were coagulated and cut (Fig. 2).

If no or low-amplitude motor responses were detected during stimulation of fascicles, the fascicles were left intact. In this case, if S1 root stimulation led to responses in the sphincter, the fascicles were left intact to prevent pelvic organ dysfunction. The S2 root was left intact in all cases. A total of 50 to 75% of the root amount was cut. When placing a bone block back in its original position, T12—L1 vertebral arches were cut; the spinous processes were cut to 2/3 of their length; and then, a vertebral arch was broken off to eliminate diastasis between the vertebral arches and the cut bone block.

After surgery, a urinary catheter was left for one day for prophylaxis of possible urinary retention. The patients were administered tramadol intramuscularly 3 times a day for 4 days to prevent pain in the postoperative period. Verticalization of patients was started on the 45th day. The patients were recommended wearing a lumbar corset when sitting and lying for 3 months. After this period, control spondylography was performed. In the absence of progressive deformities, the corset was removed. Physiotherapy was started after discharging patients from the hospital. The degree of residual flexion contractures was assessed three 3 months after surgery, and a decision on orthopedic surgical treatment was made.
Clinical cases

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<th>Muscle tone before</th>
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</table>

**Results**

In all cases, a reduction in abnormal muscle tone in the adductor muscles, gastrocnemius muscles, and hamstring muscles from 4.34±0.53 preoperatively to 1.61±0.45 postoperatively (p<0.001), on average, was observed in the early postoperative period. An increase in the range of passive movements in the hip, knee, and ankle joints was observed in association with regression of myogenic contractures. However, no changes in locomotor functions were observed in the early postoperative period. In 4 cases, delayed urination for
Figure 1. Positioning of electrodes for intraoperative myography.

Figure 2. Coagulation of fascicles.

2—3 days occurred in the early postoperative period. After this period, the disturbances resolved spontaneously.

An examination of patients after 3 months revealed an increased range of passive movements in all cases. In 21 (44%) cases, an increased range of active movements (flexion and extension in the knee and hip joints, increased dorsiflexion of the foot) was also observed. Contractures in the ankle and knee joints remained in 15 patients, which required additional orthopedic surgery on the lower extremities.

The changes in locomotor functions were observed 6 months after surgery. In the long-term follow-up (2 or more years after surgery), the total change in locomotor function was 3%: from $27\pm 12\%$ before surgery to $30\pm 13\%$ after surgery ($p<0.009$). The greatest change was observed in class 3 patients (GMFM scale) where it was 4%: from $48\pm 4\%$ before surgery to $52\pm 6\%$ after surgery ($p<0.042$). The changes in class 4 patients were less significant and amounted to 2%: from $29\pm 5\%$ before surgery to $31\pm 6\%$ after surgery ($p<0.001$). In class 5 patients, improvements were minimal — only 1%: from $12\pm 4\%$ before surgery to $13\pm 5\%$ after surgery ($p<0.068$) (Fig. 3).

According to the Ashworth’s scale, the changes in muscle tone in these subgroups were similar: 2.64 in class 3 (from $4.28\pm 0.39$ to $1.64\pm 0.24$); 2.84 in class 4 (from $4.61\pm 0.5$ to $1.77\pm 0.69$); 2.59 in class 5 (from $4.22\pm 0.54$ to $1.63\pm 0.51$) (Fig. 4).

The best functional results were obtained in children under 10 years of age. The overall change in the locomotor status varied from $29\pm 14\%$ before surgery to $32\pm 17\%$ in the long-term period ($p<0.057$). The locomotor function status in three patients from this group was upgraded by 1 point (GMFM scale): 1 patient upgraded from class 5 to class 4; 2 patients were upgraded from class 3 to class 2. No significant changes in the locomotor status were observed in patients older than 14 years of age.

A analysis of correlation between the amount of cut root fascicles and the changes in muscle tone and locomotor functions revealed a direct relationship only between the percentage of cut roots and spasticity regression ($r=0.85$). No direct relationship between the amount of cut root fascicles and changes in the locomotor status was found.

Four cases of spastic syndrome recurrence were observed in the long-term period. In two cases, spasticity relapsed only in the gastrocnemius and adductor muscles and did not reached the preoperative level. The state of another two patients returned to the preoperative level. A persistent clinical effect was observed in the other cases.

In one case, wound CSF leakage developed on the 3$^{rd}$ postoperative day. In this connection, a lumbar drain was used for 5 days, which resulted in elimination of the leakage; the wound healed by primary intention. There was no progression of spinal deformity in any case.

Discussion

Our findings demonstrate that selective dorsal rhizotomy is an effective technique for reducing severe spastic syndrome in CP patients. Spasticity resolves immediately after surgery, and the effect is persistent in most cases for many years [9, 10].

The study showed that the greatest changes in the locomotor status are typical of class 3 patients (GMFM scale). Similar results were reported in papers of other authors [11, 12].

The GMFM scale predicts the efficacy of planned surgery and defines the limits of outcomes that can be achieved in each particular case. The goal of treatment of class 5 patients is to facilitate the care for the patients and prevent gross deformities of the musculoskeletal system. In this group of patients, no significant changes in the locomotor status can be achieved; the child’s parents should be first informed of this problem. Class 4 patients may develop positive changes in locomotor functions
and learn new motor skills; unfortunately, the rehabilitation capabilities in this group of patients are limited. Class 3 (GMFM scale) has the most favorable prognosis. These patients will be capable of walking on their own [13, 14].

An important predictor of the surgery efficacy is the patient age. According to our findings, the greatest changes in the locomotor status were typical of patients under 10 years of age. The importance of early rhizotomy is also emphasized in a number of works by other authors. The preschool age, up to 7 years, is believed to be optimal [15—17]. Indeed, gross fixed contractures do not form at this age, and patients after correction of spastic syndrome will likely not require orthopedic interventions [18]. Furthermore, the movement pattern forms in this period, which makes rehabilitation treatment most effective. In patients older than 10 years of age, the changes in the locomotor status were less significant, while no changes occurred in patients older than 14 years of age. Therefore, rhizotomy in adolescent patients is palliative treatment.

Fig. 3. Changes in locomotor functions in patients of classes 3, 4, and 5 (GMFM scale).
aimed just to facilitate care and reduce pain associated with spasticity [19].

Various studies report different data on the amount of sensory root resection, ranging from 50 to 75% [20, 21]. In this study, we analyzed a relationship between the amount of cut root fascicles and the changes in muscle tone and locomotor status. The amount of root resection was found to directly affect muscle tone. The greater the amount of cut root fascicles was, the larger the changes in spasticity were. This is quite logical because the greater the number of cut myotatic fibers is, the less the afferent activation of alpha motor neurons is. However, no direct relationship between the amount of cut roots and the changes in locomotor functions was found. This confirms...
the fact that reduced spasticity is not the only requirement for improving motor skills. The disease severity, age of surgery, mental development level, rehabilitation treatment, and others factors also affect motor skills. However, an insufficient amount of cut fascicles leads to that spasticity may persist in some muscle groups and interfere with further rehabilitation. On the other hand, excessive resection of fascicles may result in muscle weakness, which will deteriorate the locomotor status of the patient. Therefore, it is important to determine the amount of dorsal root resection in each particular case. All the time, we relied on EMG control results: only those fascicles were cut that produced high amplitude responses in several muscle groups or bilateral motor responses. Fascicles producing low-amplitude responses or responses in one muscle group only were left intact. In the long-term period, we had 4 (8.5%) cases of spasticity recurrence. The mean amount of dorsal root resection in these patients was 60±3.56%, which was significantly lower than the mean amount of resection in the entire group — 69±5%. This suggests that a sufficient amount of fascicles should be cut for achieving a sustained clinical effect. The same conclusion is made in other studies on this topic. The amount of root resection in rhizotomy at the lumbar level should be at least 65%, otherwise spasticity is likely to relapse.

In contrast to a number of other studies [22—24], no further progression of spinal cord deformity was observed in patients from our series of operations. We believe this is associated with the used laminotomy technique. As an approach, we used osteoplastic laminotomy of the T12—L1 arches with mandatory preservation of the articular processes. In all cases, before placing the bone block back in its original position, the vertebral arches were cut to eliminate diastasis between the block and arches. Therefore, we fully preserved the structures of the posterior supporting complex of the spinal cord.

### Conclusion

Selective dorsal rhizotomy is an effective technique for improving spasticity. The degree of a muscle tone reduction depends directly on the amount of cut fascicles. In addition to decreased muscle tone, the functional outcome of rhizotomy is also affected by the patient’s baseline functional status and age of surgery. In any case, the operation should be performed under EMG control, and the amount of root resection should also be taken into account. Osteoplastic laminotomy should be used as an approach for preventing spinal cord deformities.

**Authors declare no conflict of interest.**

### REFERENCES

Various cerebral palsy (CP) forms are predominated by spastic palsies where lower extremity spastic paraparesis is the basic syndrome. So far, 20 to 42% of treatment outcomes in patients with normal intelligence remain unsatisfactory.

Management of abnormal muscle tone is the main problem in the treatment of CP patients. Functional neurosurgery techniques may be recommended for use at a certain stage if conservative treatments fail.

At present, selective dorsal rhizotomy at the level of dorsal lumbar and upper sacral roots, which was developed by W. Peacock and L. Arens in 1982, is most often used for treatment of patients with lower extremity spastic paraparesis. The operation involves separation of the dorsal roots into fascicular groups and cutting of those producing abnormal motor responses in the form of tonic muscle contraction during stimulation. At the same time, some issues associated with the use of this treatment technique still remain poorly understood. Most authors described not so much contraindications as conditions where the surgery effect was ambiguous and noted adverse effects of the surgery on locomotor functions of patients who used their spasticity for supporting or walking. Orthopedic complications associated with laminectomy have been insufficiently covered in the literature; there are only a few mentions of such a possibility.

Having studied long-term outcomes by means of the GMFM 88 comprehensive evaluation scale, the authors determined the surgery effect in terms of locomotor function preservation and spasticity reduction. The article describes in detail the surgical technique and methodology of neuromonitoring. The authors pay special attention to the problem of spinal deformities at the thoracolumbar junction as well as to the methods of laminoplasty and preservation of the intervertebral joints for the stability purpose. In conclusion, the authors summarize up the results of work and provide recommendations for the optimal age of the intervention, amount of fascicle resection, and expected time of surgery-based improvements.

The work used modern methods of statistical analysis of a significant amount of the international literature data. However, the authors did not mention a study by A.Yu. Stepanenko (1996), whose thesis topic is the same as the article title. That study carried out at the same institution 20 years ago contains recommendations for the optimal age of the operation (6—10 years), describes a relationship between the amount of cut fascicles (at least 65%) and the spasticity reduction degree, and covers the issues of spinal stability preservation in these interventions. The work of 1996 was based on technologies used in selective dorsal rhizotomy that were put into 3 inventions and innovations. In general, the efficacy of this technique achieves similar levels — 27—40%.

It should be noted that methods of functional surgery, being a part of comprehensive treatment of children with severe cerebral palsy, significantly improve the patient’s quality of life and require consolidation of knowledge and methods of surgery in terms of experience accumulation and analysis of the results of foreign and domestic research.

A.O. Gushcha (Moscow, Russia)
Electromyographic Control of Botulinum Toxin A Injections in the Upper Limb Muscles in Patients with Spasticity of Various Etiologies

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1Burdenko Neurosurgical Institute, Moscow, Russia; 2Sechenov First Moscow State Medical University, Moscow, Russia; 3Medical and Rehabilitation Center, Moscow, Russia

Aim. The study aim was to investigate the efficacy of botulinum toxin A injections under EMG control in patients with upper limb spasticity of various etiology for decreasing muscle tone and improving the passive limb function as well as to assess the possibility of a botulinum toxin dose reduction under combination of these techniques. Material and methods. Sixty one patients with upper limb spasticity of various etiologies were evaluated. All patients underwent treatment at the Rehabilitation Department of the Burdenko Neurosurgical Institute in the period between 2009 and 2014. The main group consisted of 29 patients administered the abobotulinum toxin A (botulinum toxin type A (BTXA), 500 U per vial) under EMG control. The control group consisted of 32 patients administered BTXA without EMG control. A repeated BTXA injection was performed on the 4th month of the study. Patients in both groups received standard rehabilitation therapy. The spasticity pattern was determined using the Arm Spasticity Pattern (ASP) scale. Evaluation of the treatment efficacy was performed using the modified Ashworth scale (upper limb spasticity evaluation), modified Barthel Index scale (life quality evaluation), Disability Assessment Scale (DAS), and Clinical Global Impression (CGI) scale. Results. The main spasticity patterns in patients of the main and control groups were as follows: the type III pattern was in 13 (44.8%) and 17 (53.1%) patients, respectively; the type I pattern was in 9 (31.0%) and 9 (28.1%) patients, respectively; the type VI pattern occurred in 7 (24.2%) and 6 (18.8%) patients, respectively. A significant improvement was observed in both groups one month after the BTXA treatment start. However, the improvement in the main group was more pronounced compared to that in the control group (p<0.05). This difference persisted throughout the whole treatment period (p<0.05). The DAS score demonstrated an improvement in both groups, but only patients of the main group had a statistically significant improvement in putting the arm through a sleeve (p<0.05). The use of EMG control reduced an administered BTXA dose by 50—300 U. Conclusions. BTXA injections under EMG control in upper limb spasticity patients may improve the treatment efficacy.

Keywords: upper limb spasticity, botulinum toxin, electromyography.

Spasticity is a motor disorder being a symptom of the upper (located in the cerebral cortex) motor neuron syndrome. Spasticity is characterized by a velocity-dependent increase in the stretch reflex (muscle tone) and is accompanied by an increase in tendon reflexes, resulting from hyperexcitability of stretch receptors [1].

Spasticity is one of the most disabling consequences of many neurological diseases, including acute cerebrovascular accident (ACVA), traumatic brain injury (TBI), brain tumors, etc. [2, 3]. Spasticity significantly reduces patients’ quality of life, is often accompanied by pain, and can cause restriction of limb movements, damage to the skin, and self-care problems. In the long-term period, spasticity may lead to fixed contractures, which significantly limits the capabilities of rehabilitation of these patients, complicates care for them, and ultimately increases the cost of treatment.

Spasticity developing in the upper limb is the most deconditioning and poorly treatable symptom. In recent years, traditional physiotherapeutic approaches to the treatment of spasticity have been supplemented by a variety of methods, including injections of the botulinum toxin type A (BTXA) that has demonstrated its safety and efficacy in reducing muscle tone in focal spasticity of the upper limb after stroke and injury and in improving the passive upper limb function [4, 5]. The data of recent studies [1, 4] indicate also a possible efficacy of botulinum toxin therapy in improving the active upper limb function.

In recent years, special attention has been paid to the botulinum toxin injection accuracy. For this purpose, a variety of injection visualization and control techniques have been used: ultrasound, electromyography (EMG), electrical stimulation (ES), and, in some cases, computed tomography (CT). However, there is now no consensus on the most effective injection technique [6]. A number of studies have demonstrated that relying on the anatomical landmarks only for making injections is not sufficient, while the use of ultrasound, ES, and EMG control improves the injection accuracy and, most importantly, treatment efficacy.

Botulinum toxin injection control using electromyography helps a doctor-injector and is recommended for injections into small and hard-to-reach muscles of the upper limb, in challenging situations, in the presence of co-contraction symptom, as well as in cases of an insufficient efficacy of previous injections. EMG control is implemented by means of either classic needle electromyography or Synopsis MIST portable electromyographs; the latter are particularly convenient for the routine daily use, do not require special long-term training, and are equipped with special needles for botulinum toxin introduction. This device transmits the
bioelectrical activity of muscles to headphones or portable speakers. Using the specific myogram audio parameters (characteristic noise of the end plates in the presence of spontaneous locomotor activity), the doctor can correctly verify the injection site (the louder sound is associated with the site of the greatest motor plaque accumulation), which gives an indication of an indirect muscle activity (passive monitoring). If necessary, a stimulation mode, which is available in the device, can be selected for stimulating the muscle to ensure, active monitoring [6, 7], accurate identification of an affected area of the target muscle [8].

The accuracy of a drug injection into the muscle selected based on clinical indications is an important aspect of botulinum toxin therapy. Therefore, it is important to know exactly the topographical features of muscles forming a particular abnormal pattern and to determine the optimal injection sites, number of points, and the drug dose for each muscle.

There are several upper limb spasticity patterns (Table 1). The most common 5 types of the upper limb patterns are as follows: type I — an adducted and internally rotated shoulder; type II — a flexed elbow; type III — a flexed wrist; type IV — a pronated forearm; type V — a clenched fist.

In addition, three forms of hand spasticity are distinguished: 1) a spastic flexed hand; 2) a claw-shaped hand; 3) an internal worm-like hand [9–11].

Each of the patterns is formed by several muscles. For example, the flexed elbow pattern is formed by 3 muscles: m. biceps brachii, m. brachialis, and m. brachioradialis, which are synergists; however, the key (most spastic) muscles among them can be only the first or second muscle, and therefore, they are injected. In addition, a contribution of antagonist muscles (m. triceps brachii in this pattern) to the pattern formation can not be ignored. The muscle activity enables implementation of an EMG examination conducted during the injection. To date, there is no unified approach to the choice of muscles, number of injection sites, and injection control method. Some doctors perform an intramuscular injection using a single site, while other doctors use several different sites, keeping in mind that drug diffusion from the injection site amounts to 2–3 cm, and denervation of a large muscle belly requires drug injection at several sites, especially in the case of large muscles, e.g., m. biceps brachii, where each muscle belly is injected at two sites.

The most common injected muscles are as follows: m. pectoralis major, m. biceps brachii, m. brachialis, m. brachioradialis, m. extensor carpi ulnaris, m. flexor carpi radialis, m. flexor carpi ulnaris, m. flexor digitorum superficialis, and m. flexor digitorum profundus. There is also a certain variation in drug doses for each muscle.

For example, doses can vary for the same muscle, depending on the spasticity degree. However, the European consensus on botulinum toxin therapy [12] recommends 125 U as the maximum and safe drug dose for an injection into one site and 1,000 U as the total drug dose for one injection into the whole upper limb.

It should also be noted that not every spasticity pattern requires botulinum toxin therapy. In this regard, setting personalized and realistic goals for each patient before treatment is an very important task.

Currently, an algorithm for botulinum toxin therapy of spasticity has been suggested [13].

1. Setting goals that should be specific, measurable, achievable, realistic, and time-specific (SMART principle).
3. Injection accuracy (use of EMG, ultrasound, or ES).
4. Combining specific physical treatments with botulinum toxin injections.

In recent years, a considerable number of international papers on the injection accuracy problem have been published, while the number of Russian publications on this subject is small. And the question still remains open: whether BTXA injections under EMG control are able to lead to better functional outcomes and to improve the efficacy of treatment of patients with upper limb spasticity. The question requires further research [14, 15].

The study aim was to investigate the efficacy of combined use of botulinum toxin type A injections and EMG control using a MIST portable device in patients with upper limb spasticity of various etiologies in order to reduce muscle tone and improve the passive limb function as well as to determine the possibility of reducing a botulinum toxin dose under combination of these methods.

**Material and Methods**

The study included 61 patients aged from 34 to 68 years with upper limb spasticity due to ACVA, TBI, or brain tumor (Table 2). All patients were treated at the Rehabilitation Department of the Burdenko Neurosurgical Institute in the period between 2009 through 2014.

The inclusion criteria were as follows: absence of earlier BTXA injections; patients’ age of 18 to 70 years; spasticity severity of more than 2 points on the modified Ashworth scale [16]; no infectious disease within 1 month before study enrollment; no surgical interventions on the involved muscle in the medical history; spasticity duration from 0.5 to 1.5 years.

The patients were divided into two groups: the main group where EMG control was used during botulinum toxin injections; the control group where injections were performed relying on the anatomical landmarks only.

In the main group, an injection of BTXA (abobotulinum toxin type A, botulinum toxin type A, 500 U per vial) was performed under EMG control by a MIST
multifunction portable device using a Bo-ject needle disposable monopolar electrode with the output, 50×0.46 mm in size. The EMG device facilitated identification of the target muscle. During an injection, the needle electrode, which is an amplifier of the device, transmits a sound signal, which characterizes the muscle bioelectric activity, to an acoustic speaker, and the doctor hears and evaluates the degree of muscle activity at various sites. Therefore, EMG control enables identification of the most spastic areas in muscles involved in the pattern in order to perform injections exactly into the areas.

Evaluation of the treatment effect was performed after 1, 4, and 8 months. Patients in both groups received a standard set of physical rehabilitation procedures: physical therapy, postural management, and massage.

The pattern of upper limb spasticity was determined using the Arm Spasticity Pattern (ASP) scale [15]. Muscle tone was evaluated using the Ashworth scale, and the habitual activity level was evaluated using the Modified Barthel Index [17]. The Disability Assessment Scale (DAS) [18] was used to evaluate the effect of spasticity on important aspects of the patient’s life: hygiene, dressing, limb position, as well as the presence of pain. In addition, a caregiver filled up the Clinical Global Impression (CGI) form [19].

Statistical processing of the study results was carried out using Microsoft Excel as well as Biostat (Publishing House Praktika, 2006) and SPSS 15.0 and Statistica 8.0 for Windows (Stat Soft Inc, USA) statistical software. The differences were considered statistically significant at \( p<0.05 \).

### Results

According to the ASP scale (Table 1), the most common spasticity patterns in the study were as follows: the type III pattern (upper limb with a flexed elbow and flexed wrist) occurred in 13 (44.8%) and 17 (53.1%) patients in the main and control groups, respectively; the type I pattern (an adducted and internally rotated shoulder) was in 9 (31.0%) and 9 (28.1%) patients of the

### Table 1. Patterns of arm spasticity

<table>
<thead>
<tr>
<th>Joint</th>
<th>Pattern</th>
<th>Relevant muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Internal rotation/adduction</td>
<td>M. pectoralis major, M. teres major</td>
</tr>
<tr>
<td>Elbow</td>
<td>Flexion</td>
<td>M. brachialis, M. biceps brachii, M. brachioradialis</td>
</tr>
<tr>
<td>Wrist</td>
<td>Flexion</td>
<td>M. flex. carpi ulnaris, M. flex. carpi radialis</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>Internal rotation/adduction</td>
<td>M. pectoralis major, M. teres major</td>
</tr>
<tr>
<td>Elbow</td>
<td>Flexion</td>
<td>M. brachialis, M. biceps brachii, M. brachioradialis</td>
</tr>
<tr>
<td>Wrist</td>
<td>Extension</td>
<td>M. ext. digitorum, M. ext. carpi radialis, M. ext. carpi ulnaris</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>Internal rotation/adduction</td>
<td>M. pectoralis major, M. teres major</td>
</tr>
<tr>
<td>Elbow</td>
<td>Flexion</td>
<td>M. brachialis, M. biceps brachii, M. brachioradialis</td>
</tr>
<tr>
<td>Wrist</td>
<td>Neutral position</td>
<td>M. flex. carpi ulnaris, M. flex. carpi radialis, M. ext. digitorum, M. ext. carpi radialis, M. ext. carpi ulnaris</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>Internal rotation/adduction</td>
<td>M. pectoralis major, M. teres major</td>
</tr>
<tr>
<td>Elbow</td>
<td>Flexion</td>
<td>M. brachialis, M. biceps brachii, M. brachioradialis</td>
</tr>
<tr>
<td>Wrist</td>
<td>Flexion</td>
<td>M. flex. carpi ulnaris, M. flex. carpi radialis</td>
</tr>
<tr>
<td></td>
<td>Pronation</td>
<td>M. pronator teres</td>
</tr>
<tr>
<td><strong>Type V</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>Internal rotation/adduction</td>
<td>M. pectoralis major, M. latissimus dorsi, M. teres major</td>
</tr>
<tr>
<td>Elbow</td>
<td>Extension</td>
<td>M. triceps brachii</td>
</tr>
<tr>
<td>Wrist</td>
<td>Flexion</td>
<td>M. flex. carpi ulnaris, M. flex. carpi radialis</td>
</tr>
<tr>
<td><strong>Spastic flexed hand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers (metacarpophalangeal joints)</td>
<td>Flexion</td>
<td>M. flex. digit. superficialis, M. flex. digit. profundus, Mm. interossei/lumbricales</td>
</tr>
<tr>
<td><strong>Claw-shaped hand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers (metacarpophalangeal joints)</td>
<td>Extension</td>
<td>M. ext. digitorum, M. ext. indicis, M. ext. digitii minimi</td>
</tr>
<tr>
<td>Fingers (phalangeal joints)</td>
<td>Flexion</td>
<td>M. flex. digit. superficialis, M. flex. digit. Profundus</td>
</tr>
<tr>
<td><strong>Internal worm-like hand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers (metacarpophalangeal joints)</td>
<td>Flexion</td>
<td>M. flex. digit. superficialis, M. flex. digit. profundus, Mm. interossei/lumbricales, M. abductor digitii minimi</td>
</tr>
<tr>
<td>Fingers (phalangeal joints)</td>
<td>Extension</td>
<td>M. ext. digitorum, M. ext. indicis, M. ext. digitii minimi</td>
</tr>
</tbody>
</table>
Table 2. General characteristics of study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Main group (n=29)</th>
<th>Control group (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.8±12.4</td>
<td>40.7±11.9</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>12 (41.4%)</td>
<td>14 (43.8%)</td>
</tr>
<tr>
<td>Females</td>
<td>17 (58.6%)</td>
<td>18 (56.2%)</td>
</tr>
<tr>
<td>Etiology of spasticity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACVA</td>
<td>13 (44.8%)</td>
<td>15 (46.9%)</td>
</tr>
<tr>
<td>Space occupying lesion</td>
<td>7 (24.1%)</td>
<td>9 (28.1%)</td>
</tr>
<tr>
<td>TBI</td>
<td>9 (31.1%)</td>
<td>8 (25.0%)</td>
</tr>
<tr>
<td>Number of months after spasticity onset</td>
<td>12±5</td>
<td>11±7</td>
</tr>
<tr>
<td>Total BTXA dose</td>
<td></td>
<td>750—1,500 U</td>
</tr>
<tr>
<td>Ashworth scale</td>
<td>2.71±0.34</td>
<td>2.64±0.59</td>
</tr>
<tr>
<td>Barthel scale</td>
<td>45.26±7.81</td>
<td>47.03±6.23</td>
</tr>
</tbody>
</table>

Table 3. Therapy-associated changes on the Ashworth and Barthel scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Group</th>
<th>Examination after treatment start, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>after 1 m</td>
</tr>
<tr>
<td>Ashworth</td>
<td>Main</td>
<td>0.94±0.37*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.19±0.54</td>
</tr>
<tr>
<td>Barthel</td>
<td>Main</td>
<td>58.14±8.71*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>51.63±7.32</td>
</tr>
<tr>
<td>DAS</td>
<td>Main</td>
<td>0.94±0.07*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.02±0.12</td>
</tr>
</tbody>
</table>

Footnote. * p<0.05 — significant differences between the main and control groups.

Table 4. Dynamics of changes in the passive limb function on the CGI scale

<table>
<thead>
<tr>
<th>Upper limb function</th>
<th>Group</th>
<th>Examination time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>Hand washing</td>
<td>Main</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>Nail cutting</td>
<td>Main</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>8 (25.0%)</td>
</tr>
<tr>
<td>Putting the arm through a sleeve</td>
<td>Main</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>13 (40.6%)</td>
</tr>
<tr>
<td>Placing a splint</td>
<td>Main</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>15 (46.9%)</td>
</tr>
</tbody>
</table>

Footnote. * — significant differences between the main and control groups before and 1 month after the treatment start, # — significant differences between the main and control groups 1 month after 2 BTXA injections.

main and control groups, respectively; the type VI pattern (a spastic flexed hand) was in 7 (24.2%) and 6 (18.8%) patients in the main and control groups, respectively. For this reason, BTXA injections were performed into appropriate muscles in various combinations (Table 1).

Four weeks after the first BTXA injection, a statistically significant decrease in muscle tone and an improvement in the passive upper limb function were observed in both groups (p<0.05), but patients of the main group had more pronounced changes compared to those in the control group (p<0.05). However, no differences between the groups were observed after 4 months because of expiration of the drug clinical effect.

In association with rehabilitation therapy, a reduction in muscle tone in main group patients administered BTXA under EMG control was statistically significantly higher than that in patients without EMG control 4 weeks after the second BTXA course. Eight months after the study start, patients of the main group had statistically significant differences on the Barthel and DAS scales, indicating a higher efficiency of BTXA injections under EMG control (Table 3).
A caregivers’ survey revealed that patients in both groups experienced a significant improvement in placing a splint as early as one month after the first and then second BTXA injections \((p<0.05)\). Patients of the main group also had a statistically significant improvement \((p<0.05)\) in putting the arm through a sleeve, while the positive changes observed in the control group were not significant. An improvement in hygienic measures (hand washing, nail cutting) was not statistically significant (Table 4).

Table 4 presents the data provided by caregivers at the study end (after eight months). An improvement in the passive limb function was found to be 1.96 and 1.82 times more frequent in patients of the main and control groups, respectively. However, the differences were not statistically significant, which may be due to the small sample size (Figure).

Given the results of other authors [15], we reduced a planned BTXA dose in 8 (27.6%) patients of the main group (with EMG control) by 50–300 U (Table 5), which did not worsen the treatment results.

**Conclusion**

This study demonstrated a good efficacy of BTXA injections under EMG control, which led to a reduction in increased muscle tone and an improvement in the passive function of the upper limb (compared to injections performed relying on the anatomical landmarks only). Furthermore, the use of EMG control reduced the botulinum toxin dose due to a more accurate analysis of injected muscle activity.

A number of previous studies demonstrated the important role of the exact needle localization in the target muscle, drug injection in the immediate proximity to the myoneural junction, and diffusion of the botulinum toxin within the appropriate area of the target muscle [20, 21]. The lack of the botulinum toxin injection effect in spasticity treatment may also result from an inaccurate injection into the target muscle and drug diffusion to adjacent muscles.

For example, a study [22] demonstrated the efficacy of botulinum toxin injections for decreasing muscle tone in the biceps muscle of the upper limb. A better effect of directed botulinum toxin injections was observed: a greater decrease in muscle tone, reduced co-contraction phenomenon, and increased range of active elbow extension in the case of directed drug administration into the endplate region under EMG control and in combination with large drug dilution compared to undirected injections with low drug concentrations.

In the present study, we used a standard dilution volume of 2.5 mL per vial; the number of injection sites was related to the muscle belly volume (1–4 sites, on average); drug doses were less than the mean doses recommended by the Consensus, which prevented side effects.

The European Consensus for the use of botulinum toxin therapy in spasticity suggests the necessity for further research to determine the most accurate techniques improving the efficacy of botulinum toxin injections because there are no comparative studies evaluating the accuracy of anatomical landmark-based botulinum toxin injections and the accuracy of botulinum toxin injections under ES and ultrasound control in adults with focal upper limb spasticity [12]. However, many specialists who use BTXA believe that injections do not require EMG control, except cases with complicated palpatory identification of the muscles. They also believe that the use of portable devices for EMG control

**Table 5. Planned and injected BTXA doses in patients of the main group**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Spasticity pattern</th>
<th>Planned BTXA dose, U</th>
<th>Injected BTXA dose, U</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>I</td>
<td>750</td>
<td>700</td>
</tr>
<tr>
<td>3</td>
<td>II</td>
<td>1,000</td>
<td>750</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>1,000</td>
<td>800</td>
</tr>
<tr>
<td>8</td>
<td>III</td>
<td>750</td>
<td>700</td>
</tr>
<tr>
<td>14</td>
<td>III</td>
<td>750</td>
<td>700</td>
</tr>
<tr>
<td>17</td>
<td>I</td>
<td>1,500</td>
<td>1,200</td>
</tr>
<tr>
<td>23</td>
<td>III</td>
<td>1,000</td>
<td>850</td>
</tr>
<tr>
<td>26</td>
<td>II</td>
<td>1,500</td>
<td>1,250</td>
</tr>
</tbody>
</table>
unreasonably increases discomfort for the patient, injection duration, and procedure cost [23, 24].

The present study clearly demonstrated that the use of EMG control during an injection in patients with upper limb spasticity led to a significantly better effect regarding a muscle tone reduction and an improvement in the passive upper limb function by more than 15%. Furthermore, EMG control did not cause significant discomfort and, in general, reduced the procedure cost through decreasing a drug dose.

**Findings**

The optimal variant of botulinum toxin injections is their combination with electromyographic control, which may increase the efficacy of treatment of patients with upper limb spasticity. However, further research using a larger sample size is needed to determine, in particular, the minimum effective botulinum toxin doses because this is extremely important due to the prevalence of this problem.

**Authors declare no conflict of interest.**

**REFERENCES**

Commentary

The topicality of the study is doubtless because the work is devoted to optimization of the management of patients with upper limb spasticity developed after common diseases, such as acute cerebrovascular disease, traumatic brain injury, and brain tumor. All professionals engaged with this issue are familiar with the complexity of rehabilitation of these patients.

One of the most modern and effective methods of treatment of upper limb spasticity is the use of the botulinum toxin. Its advantages include the effect locality, injections in any accessible area, effect duration, and lack of systemic adverse events. Botulinum toxin injections in spasticity patients lead to elimination of muscle hypertonus, which greatly facilitates the rehabilitation measures aimed at recovery of a motor deficit and significantly improves self-care or complex care for patients with this pathology. In this case, administration of the drug under electromyographic control showed a high efficacy associated with the fact that the drug is administered in the immediate proximity to the most tight muscle area. These important issues are addressed in the present work, which makes the problem topical and socially significant and defines the study aim to assess the efficacy of botulinum toxin therapy under EMG control in upper limb spasticity.

The reliability of the findings is confirmed by a sufficient amount of the studied material, application of goal-relevant techniques, and use of modern methods of statistical analysis. The results obtained by the authors using modern methods of research indicate achieving the study objectives. The data on a reduction in the planned drug dose due to electromyographic control are of particular interest.

The findings may be very useful to practitioners: neurologists, neurosurgeons, specialists in neurorehabilitation because electromyographic control will provide significant optimization of treatment of spastic patients.

I would like to wish the authors to follow the chosen direction and continue research, but also pay attention to another method used for accurate BTXA injections, namely ultrasonic control.

In general, the article is topical and is of scientific and practical novelty.

V.L. Golubev (Moscow, Russia)
Results of Motor Cortex Stimulation in the Treatment of Chronic Pain Syndromes

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

Aim. The article is aimed to demonstrate our experience in motor cortex stimulation (MCS) in patients with chronic neuropathic pain syndromes, assess the clinical efficacy of the technique in short-term and long-term follow-up, and analyze potential predictors of the MCS efficacy. Material and methods. Twenty patients were implanted with MCS electrodes at the Burdenko Neurosurgical Institute in the period between 2004 and 2014. The mean age of patients was 52 years (26 to 74 years). The patients suffered from neuropathic pain syndromes of different genesis (post-stroke, multiple sclerosis, atypical facial pain, phantom limb pain, brachial plexus injury, spinal cord injury, complex regional pain syndrome I). All patients underwent neurological examination with verification of neuropathic pain (DN4, Pain Detect, LANSS). The pain intensity and its effect on quality of life were assessed before operation and during follow-up according to 10-point visual-analog scales (modified Brief Pain Inventory). Before surgery, all patients underwent several repetitive transcranial magnetic stimulation (rTMS) sessions. After implantation of epidural electrodes, test MCS was performed. Results. Test stimulation was positive in 19 (95%) patients. All these patients were implanted with a chronic MCS system. The mean follow-up was 49.3 months (from 3 to 96 months). In short-term follow-up (first 6 months), a positive result of MCS was observed in 17 patients, and a reduction in the pain intensity ranged from 37.5% to 90%. In long-term follow-up (from 12 to 96 months), 14 patients had positive MCS results, and a reduction in the pain intensity amounted to 25% to 60%. All patients with positive MCS results received significantly decreased doses of opioids and tramadol. Two patients developed infectious complications, but there was no neurological deficit. Analysis of the factors affecting the efficacy of motor cortex stimulation did not reveal a statistically significant effect of rTMS and the presence and intensity of motor deficit. Conclusion. Chronic epidural MCS is an effective and safety method for the treatment of some chronic neurogenic medically-refractory pain syndromes. Further research is necessary to specify the patient selection criteria and the MCS efficacy predictors.

Keywords: motor cortex stimulation, chronic pain, neuropathic pain, clinical efficacy, predictors, post-stroke pain, atypical facial pain, phantom limb pain, spinal cord injury, complex regional pain syndrome I.

Abbreviations

VAS — visual analog scale
MRI — magnetic resonance imaging
TMS — transcranial magnetic stimulation
ES — electrostimulation
DN4 (Dolour Neuropatique), LANSS (Leeds Assessment of Neuropathic Symptoms and Signs), Pain Detect — questionnaires revealing the nature of neuropathic pain
DREZ-tomy — (dorsal root entry zone) dorsal root entry zone excision
MCS (Motor Cortex Stimulation) — motor cortex stimulation
PQLC (Pain and Quality of Life Card) — pain and quality of life card (a modified brief pain inventory)

Motor cortex stimulation has been used to treat chronic pain syndromes for more than 20 years. To date, more than 1,000 publications devoted to basic and clinical research of the efficacy of motor cortex stimulation in patients with neuropathic pain syndromes have appeared worldwide. In particular, these include 4 randomized controlled trials [1—4] and 3 meta-analyses [5—7].

The indications for motor cortex stimulation are neuropathic pain syndromes when pharmacotherapy and minimally invasive surgery are ineffective. These syndromes include severe post-stroke pain, atypical trigeminal facial neuralgia, phantom pain as well as other severe deafferentation pain syndromes (brachial plexus injury pain, spinal cord injury). At present, some doubts about the MCS efficacy still remain despite the positive results of randomized controlled trials and meta-analyses [8, 9]. This requires further investigation of the efficacy of the technique and ways to improve it.

At the Burdenko Neurosurgical Institute, chronic pain syndromes have been treated using neurostimulation for more than 15 years [10, 11] and motor cortex stimulation for 11 years. The aim of this publication is to demonstrate our experience in application of motor cortex stimulation in clinical practice, evaluate the MCS efficacy in short-term and long-term follow-up, and analyze potential predictors of the MCS efficacy.

Material and Methods

At the Burdenko Neurosurgical Institute, motor cortex stimulation was used in 20 patients (10 males and 10 females) aged 26 to 74 years (mean age 52 years) in the period between 2004 and 2014. The mean duration of pain syndrome before surgery was 5 years. In all cases, the patients had persistent neurogenic pain refractory to analgesics, specific analgesic
psychotropic pharmacotherapy, physiotherapy treatments, and acupuncture. The pain syndrome characteristics for each patient, along with the patient’s gender and age, are shown in Table 1.

Below is a more detailed characterization of the clinical cases. In 4 patients, the cause for seeking treatment was the central post-stroke pain syndrome (Table 1: cases 13, 15, 19, 20). In this case, three of these patients had hemorrhagic stroke (13, 19, 20), and one patient (15) had ischemic stroke.

Among the hemorrhagic stroke patients, hemorrhage occurred directly in the thalamus in 2 patients (13, 19) and in the basal ganglia, including the thalamus, in 1 patient (20).

In one patient (10), the central pain syndrome in the left arm and left half face was associated with multiple sclerosis.

The main complaint in 4 more patients (2, 6, 9, 18) was severe facial pain. In 2 females (2, 9), facial pain developed in association with multiple sclerosis, with the pain being localized in the right half face, mainly along the 2nd and 3rd branches of the trigeminal nerve. The pain was constant, with paroxysmal aggravation. In one patient (6), facial pain appeared after dental treatment in the lower jaw. The 4th patient (19) presented with the classical clinical picture of trigeminal neuralgia on the right; however, the pain syndrome changed after pain microvascular decompression: constant background pain with paroxysmal aggravation developed.

Two patients (12, 16) suffered from phantom limb pain. One of them had traumatic amputation of the left limbs in a car accident, with the phantom pain developed both in the arm and in the leg. The second patient had a severe soft tissue burn of the left arm due to electrical injury. The phantom limb pain developed after exarticulation of the left shoulder.

In another patient (4), phantom limb pain appeared due to post-traumatic avulsion of the primary trunks of the left brachial plexus. The pain manifested as a sensation of an “extra” left arm and constant pressing, tightening, and twisting pain in the “arm”.

Severe deafferentation pain syndromes associated with brachial plexus trunk injury were observed in 4 more patients (1, 3, 8, 17). In one case, a patient (1) with preganglionic avulsion of the brachial plexus trunks underwent neurolysis of the secondary trunks of the brachial plexus and neurotization of the musculocutaneous nerve. Later, stereotactic implantation of electrodes was performed for neurostimulation to the thalamic sensory nuclei and periaqueductal gray matter. These operations had a short-term benefit.

In the 2nd case, a patient (3) had a traumatic injury of the right brachial plexus with the development of total paralysis in the arm. Suspension arthroplasty of the right shoulder joint using a lavsan tape and external neurolysis of the primary and secondary trunks of the right brachial plexus as well as selective neurotization of the musculocutaneous nerve with the 2nd and 3rd intercostal nerves were performed. The pain syndrome persisted after all operations.

In the 3rd case, a patient (8) after an injury underwent neurolysis of the primary trunks of the brachial plexus, then neurolysis of the median and ulnar nerves, and later orthopedic correction of the hand and plasty of the finger flexors.

In the 4th case (17), pain had the form of complex regional pain syndrome type II; a patient underwent surgery for the cervical spine. It is noteworthy that the patient was first implanted with a system for chronic epidural electrical stimulation of the spinal cord at the cervical thickening level as analgesic treatment. The analgesic effect of the stimulation was neutralized within several months despite repeated reprogramming of the system and the use of various ES modes.

In 2 patients (5, 11), pain arose after resection of a spinal cord tumor: an intradural extramedullary neoplasia at the C5—T2 level was removed in the first case, and a nerve root neoplasia at the C6—C7 level was resected in the second case. The first patient underwent DREZ-tomy for the pain syndrome, after which the pain initially reduced, but after 1 month began to increase again. The second patient underwent stereotactic thalamotomy, after which pain regression was observed within 3 weeks.

In one female patient (14), the cause of complex regional pain syndrome type I was long-term compression of the right arm and compression of the ulnar and median nerves. She underwent decompression of the nerves at the lower third forearm level and in the Guyon’s canal that had a short-term benefit.

A patient with a cervical spinal cord injury (7) presented with tetrasyndrome with moderate upper limb paresis (deep in the distal segments), spastic lower deep paraparesis, and dysfunction of the pelvic organs (involuntary urination and stool retention). However, the patient’s quality of life was mostly affected by pronounced deafferentation pain, mainly of the conductive nature, in the arms, chest wall, and legs as well as severe spasticity in the legs.

Preoperative examination

All patients underwent a neurological examination with assessment of pain syndrome using DN4, Pain Detect, and LANSS scales (neuropathic pain syndrome was confirmed in all patients). The assessment of the pain syndrome intensity was performed before surgery, in the postoperative period, and during follow-up using PQLC that included 10-point visual analog scales (VAS). We assessed the maximum and minimum intensity of background and/or paroxysmal pain, mean daily pain intensity, rate of pain episodes, need for analgesics as well as impact of pain on various aspects of everyday life (general condition, mood, daily activity, passive recreation, self-care, communication with others, sleep, sexual activity).

To select patients and assess the pain syndrome intensity, we used a multi-dimensional verbal-color pain test developed at the Institute of Reflexology of the Federal Research Clinical and Experimental Center of Traditional Methods of Diagnosis and Treatment [12]. This test determines the intensity of pain components using factor scales and provides an integrated quantitative (score/percentage) and qualitative estimate that reflect individual’s conscious and unconscious pain experience. The test results are conveniently presented in the graphical format. The test comprises seven scales. The first three scales are the pain intensity, pain frequency, and pain duration. The pain intensity scale is compared to the color choice: patients’ color preferences and rejections according to their own internal pain sensations are analyzed (pain intensity and pain pattern).

The scale of emotional pain perception provides a quantitative and qualitative estimate of the subjective attitude to pain. The neurotization scale evaluates the level of neurotization and the degree of involvement of behavioral components in the severity of the internal picture of patient’s disease. The adaptability scale identifies environmental factors affecting pain worsening. The lie scale determines the sincerity of patient’s responses. If the lie scale score is 5—6, the test results are recognized unreliable.

All patients underwent brain TMS, as a test procedure, in the motor cortex projection, over the area of planned
implantation of electrodes. The efficacy criterion was a reduction in pain by 50% or more at the threshold pulse values after two stimulation series of 10 bursts.

In a patient (7) with a cervical spinal cord injury and bilateral pain, the implantation side was determined by TMS. Alternative stimulation on the left and right sides was performed during outpatient clinic visits for TMS (total of 10 sessions). On this basis, a significant prevalence of bilateral analgesic and anti-spasmodic effects of TMS upon right-sided stimulation was revealed. Therefore, electrodes were implanted on the right side only.

**Surgical technique**

Preoperatively, all patients underwent brain MRI with 3D-reconstruction and functional MRI to determine the representation of pain region (arm, leg, or face) in the motor cortex (Fig. 1a), on the contralateral side with respect to the pain localization. For this purpose, patients during tests were asked to make movements in an appropriate part of the body. In the absence of movement in the extremities, the patients were asked to make virtual movements.

The data on pain area representation and 3D-reconstructed MRI images of the brain were loaded into the memory of a navigation station (StealthStation, Medtronic, USA or Brain Lab, USA) (Fig. 1b, c) where identification of anatomical coordinates and landmarks of the electrode implantation area was performed by combining these data.

Surgery was performed under total intravenous anesthesia and mechanical ventilation. To obtain adequate motor responses, muscle relaxants were restrictedly used, and the depth of anesthesia was monitored (bispectral index was calculated based on a continuously recorded electroencephalogram).

The projection of an appropriate motor cortex area and the craniotomy site were marked up on the patient’s head using the navigation station (Fig. 1d, e).

Craniotomy was performed with the formation of a free bone flap of 5×5 cm. The dura mater was not opened. The site of final implantation of two four-contact flat electrodes was identified based on the data of intraoperative electrostimulation at the subthreshold levels with detection of motor evoked potentials (Fig. 2).

After getting the motor response, the electrodes were fixed to the dura mater in such a way that two cranial contacts of each electrode were positioned anteriorly to the central sulcus, 2 caudal contacts were positioned posteriorly to the sulcus, and electrodes themselves overlapped the projection of an appropriate pain area (Fig. 3a, b). The bone flap was placed back and fixed, and soft tissues were tightly sutured. Electrode ends were tunneled out through an adapter to the skin (Fig. 3c, d). At this point, the first stage of implantation was completed.

After implantation of electrodes, the test stimulation period began that lasted for 1—2 weeks. Before its onset, subthreshold levels of the stimulation amplitude were determined by monitoring of motor evoked potentials. The appropriate electrode polarity was determined in the same way. If a stable analgesic effect of electrical stimulation (reducing the pain intensity by 50% or more) was achieved throughout the test period, the second stage (implantation of a system for chronic ES) was performed.

The second stage was also performed under intravenous anesthesia and mechanical ventilation. Electrode ends were connected through subcutaneous adapters to a pulse generator implanted subcutaneously in the subclavian area. The pulse generator was programmed in accordance with parameters of the test stimulation period. The patient was handed a desk for self-control of stimulation (switching on, switching off, and switching among programs). In the case of a negative result of the test period, epidural electrodes were removed.

Table 1. Characterization of pain syndrome in patients

<table>
<thead>
<tr>
<th>No</th>
<th>Gender</th>
<th>Age, years</th>
<th>Diagnosis</th>
<th>Pain duration, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>42</td>
<td>Differentiation pain syndrome after avulsion of the left brachial plexus nerve roots</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>64</td>
<td>Atypical facial pain. Multiple sclerosis</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>45</td>
<td>Right brachial plexopathy</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>Pain syndrome after resection of an intradural extramedullary tumor of the spinal cord</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>42</td>
<td>Left brachial plexopathy and phantom limb pain</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>39</td>
<td>Atypical facial pain. Facial anesthesia dolorosa</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>54</td>
<td>Pain syndrome after cervical cord injury</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>Brachial plexopathy</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>26</td>
<td>Atypical facial pain. Multiple sclerosis</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>50</td>
<td>Central neurogenic pain. Multiple sclerosis</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>51</td>
<td>Pain syndrome after resection of a spinal cord meningioma at the cervical level</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>46</td>
<td>Phantom limb pain (left)</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>61</td>
<td>Central pain syndrome after stroke in the right hemisphere</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>46</td>
<td>Complex regional pain syndrome type 2, neuropathy of the median and ulnar nerves</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>59</td>
<td>Central pain syndrome after stroke in the right hemisphere</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>60</td>
<td>Phantom pain of the left arm</td>
<td>7</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>60</td>
<td>Right brachial plexopathy</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>73</td>
<td>Atypical facial pain</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>59</td>
<td>Central pain syndrome after stroke in the right hemisphere</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>74</td>
<td>Central pain syndrome after stroke in the right hemisphere</td>
<td>6</td>
</tr>
</tbody>
</table>
**Postoperative and long-term follow-up**

Postoperatively, all patients were monitored for the neurological status and pain intensity level using PQLC. In the long-term period, all patients were examined at intervals of 3—6 months. Pain intensity control, correction of a stimulation program, and, if necessary, correction of pharmacotherapy were performed.

**Methods of statistical data processing**

In this publication, statistical data are presented as frequencies and percentages. A paired t-test was used to compare pain levels in patients before and after surgery. All statistical calculations were performed using the PASW Statistics software package, version 22.0, (SPSS: IBM, Chicago, IL, USA). Graphical diagrams were plotted using the Excel software from the Office Professional Plus 2013 package (Microsoft, USA).

**Results and Discussion**

According to the literature (randomized trials and meta-analyses), 36 to 80% of patients are satisfied with the motor cortex stimulation treatment [1—7].

The treatment efficacy varies for different pain syndromes. It amounts to 60—80% for the central post-stroke pain syndrome, 75—76% for atypical facial pain, 36—45% for brachial plexus injury pain, and 56—60% for spinal cord injury pain [5—7].

In this study, test stimulation had a positive effect in 19 (95%) of 20 patients implanted with epidural electrodes for motor cortex stimulation. In one patient (6), a significant decrease in the analgesic efficacy of ES was observed by the end of the test period. Despite attempts of reprogramming, the analgesic effect was not restored. For this reason, electrodes were removed.

Therefore, only 19 patients aged 26 to 74 years were implanted with a system for chronic electrical stimulation of the motor cortex (Table 2).

The mean follow-up was 49.3 months (3 to 96 months). In the short-term follow-up (within the first 6 months after implantation), the mean pain intensity decreased from 7±0.4 to 3±0.4 points (p<0.05, paired t-test) in 17 (89.5%) patients, with the regression level ranging from 37.5 to 90%. In the long-term follow-up (12 to 96 months), positive results were observed in 14 (73.7%) patients. The mean pain intensity decreased from 7±0.4 to 4.5±0.4 points (p<0.05, paired t-test); the pain regression level amounted to 25—60%.

In addition to the mean pain intensity, the patients had a statistically significant decrease in both the minimum and maximum pain intensity. There was a significant decrease in the rate and intensity of pain paroxysms. These episodes were not usually scored above 5—6 on VAS (instead of 9—10 before surgery) and were even stopped within 10—30 min upon increasing the stimulation amplitude in several patients (2, 11, 13, 15).

Stimulation parameters used in the study were as follows: amplitude: 1.0—5.5 V; frequency: 20—50 Hz; pulse width: 60—210 µs. The literature data [13, 14] are generally in accordance with ours.

The need for analgesics was significantly reduced in many patients. One patient (3) with traumatic injury of the brachial plexus trunks completely refused medication; 4 other patients (5, 9, 13, 19) reduced administration of anticonvulsants 3 times and completely refused opioid analgesics. A patient (11) with a cervical nerve root injury due to neurinoma resection reduced the tramadol dose 2 times and completely refused morphine. A patient (7) with a spinal injury reduced the dose of tramadol and sibazon 2 times. It is worth noting that all patients in whom stimulation was effective either refused or significantly reduced a dose of narcotic analgesics and tramadol.

Table 3 presents the data of medication therapy for pain syndrome that was performed before stimulation and in association with motor cortex stimulation.

All patients had a decrease in the impact of pain on various aspects of the life quality (in particular, on daily activity) (Fig. 4).

Below, we describe the results of the multi-dimensional verbal–color pain test. Before surgery, all patients had maximum scores for the rate and duration of pain (5—6). That is the pain in all patients was constant. According to the pain intensity scale, most of the patients assessed their pain as intolerable. Only one female patient (3) assessed her pain as very severe (score of 5). All examined patients, except a patient 6, were not detected with perversions of color, which indicated that a psychogenic pain component was not dominant in them. According to the scale of sensory pain perception, all patients demonstrated high pain sensitivity. Indicators of the emotional pain perception scale were very high in all patients. Two patients (3, 6) demonstrated a particularly high neurotization level (up to a score of 6). Both of them were ill for several years, and the first examination revealed their extreme fixation on their painful feelings and painful experiences. Given the specificity of our patients, of greatest importance to them were factors associated with motion and rest (posture, postural change, walking, standing, sitting, etc.) as well as with a change in the weather. Factors associated with eating, type of food, and smoking were scarcely mentioned. The lie scale score was not higher than 4 in all patients.

It should be noted that despite certain fluctuations in the ES efficacy in the early postoperative period, the analgesic effect in most patients was stable in the long-term follow-up. For example, the neurostimulation efficacy in a patient 11 in the early postoperative period (1 month after discharge) decreased by 20% compared to the baseline level, but further remained stable. At the same time, the neurostimulation efficacy in a patient 3 increased by 10% compared to the baseline level due to independent searching for an optimal stimulation program and periodical changing the ES frequency. In general, our data are in agreement with the literature data [13, 14].

**Negative results**

The stimulation system was removed in 3 patients due to loss of efficacy. For example, the stimulation efficacy in 2 patients with pain after brachial plexus root avulsion reduced significantly and did not result in a satisfactory regression of the pain syndrome. This occurred 5 and 10 months after implantation in cases 17 and 1, respectively. In the patient 1, a reduction in the pain intensity was achieved after a repeated (third) DREZ-tomy. In a patient (8) with a cervical spinal cord injury, stimulation significantly reduced the intensity of both pain and spastic syndromes; however, the duration and intensity of the effect decreased significantly within the next two years. In all cases, there were attempts to reprogram the system, but they did not improve the results.

In 2 more patients, follow-up was interrupted. One patient (2) with multiple sclerosis died from the underlying disease 5...
years after system implantation. One patient (9) stopped communicating in 2010. However, the patients in both cases reported a good efficacy of stimulation as long as they maintained contact.

Complications

According to the literature [14], the rate of complications of motor cortex stimulation is no more than 5%, on average. The most common complications of motor cortex stimulation are technical (electrode break and system failure; their cumulative rate is 5.7%) and infectious complications that are mainly associated with the wound or implantation site of a subcutaneous part of the system: their rate is 5.1% [6, 14].

A special place among complications of motor cortex stimulation is held by epileptic seizures that usually occur during intraoperative or test stimulation. Their rate is 12% [6, 14], but they occur more often in the case of subdural stimulation [6]. The most severe complications of cortical electrode implantation are epidural or subdural hematomas (depending on the electrode location) that may lead to death, but their rate is less than 1%. Also, the literature [6] reports single cases of a neurological deficit, regressing within one day or a few months after implantation of the entire system.

In our series of the 19 patients implanted with electrodes for epidural motor cortex stimulation, postoperative complications developed in 2 (10.5%) patients. In both cases, these were infectious complications that did not lead to a sensory or motor deficit or worsening of pain. Three months after implantation of the system, a patient 20 developed purulent inflammation in the pulse generator pocket and a decubitus ulcer over the connector implantation site. The system was removed despite a good analgesic effect. In another patient (12), a decubitus ulcer formed at the site of pulse generator implantation 3 years after surgery, which required removal of the generator together with connectors.

While discussing the results, we should note that the present study has several limitations precluding us from making comprehensive conclusions. The sample of patients was not
Fig. 2. Electrode implantation technique.

Intraoperative electrophysiological monitoring.

- a, b, c — location of needle electrodes in the muscles of the face, hand, and feet; d — intraoperative stimulation; e — M-response from the facial muscles; f — response from the hand.
large enough \((n=20)\). In addition, the genesis of pain in all patients was clearly different (central pain syndrome in some patients, while both central and peripheral pain syndrome in others) despite the common features (deafferentation pain). This limits us in making general conclusions for all patients. At the same time, allocating the patients into disease subgroups is impractical due to the small sample size. However, it should be noted that the number of patients in many international trials conducted at a single clinical site did not exceed 30 patients even for a 10-year period [1, 3, 15—17]. Large samples (over 100 patients) usually occur only in multicenter trials and meta-analyses [5—7]. This problem is associated with a strict limitation on the range of diseases that serve indications for motor cortex stimulation as well as with their relatively low prevalence.

In the present study, like in most other studies [15, 17], no placebo-controlled stimulation was performed. Particular attention should be paid to the past medical history of our patients, in particular to the availability of adequate medical treatment. This need stems from the fact that an important indication for motor cortex stimulation, along with pathogenesis and a clinical form of pain syndrome, is resistance to pharmacotherapy. Meanwhile, a study conducted in Europe [18] showed that the real drug-resistant neuropathic pain, as defined by international experts, is found only in 5% of patients. A significant proportion of patients with persistent neuropathic pain syndromes have no adequate therapy.

Analysis of the data on conservative treatment in our patients (Table 3) reveals that there were patients who received adequate pharmacological treatment with some delay (1, 3, 6, 8, 11, 13—18, 20) or did not receive it at all (5, 7). For example, a patient 17 was immediately prescribed with tramadol in tablets and injections. He had taken the medication for at least 10 years, after which attempts of adequate treatment using anticonvulsants and antidepressants failed. In addition, the patient underwent a destructive intervention for the cervical roots and thoracic sympathectomy in the absence of adequate medical treatment. The efficacy of motor cortex stimulation in this patient quickly decreased (within 5 months after implantation).

Investigation of predictors for the motor cortex stimulation efficacy in treatment of neuropathic pain syndromes is of great significance. The literature provides ambiguous data on this problem [14]. Criteria that have been used for a long time since
### Table 2. Demographic indicators and results of stimulation in long-term follow-up

<table>
<thead>
<tr>
<th>Demographic indicator</th>
<th>Mean ± SD</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic indicator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years</td>
<td>53±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender ratio, m/f</td>
<td>1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of pain history, years</td>
<td>5±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive test stimulation (n), %</td>
<td>19 (95%)</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Negative test stimulation (n), %</td>
<td>1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of long-term follow-up, months</td>
<td>65±22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of regression of the mean pain intensity in long-term follow-up</td>
<td>4.3±1.1</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Decrease in the maximum pain intensity during follow-up, VAS score</td>
<td>2.7±1.3</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Decrease in the minimum pain intensity during follow-up, VAS score</td>
<td>3.6±1.4</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Decrease in the rate of paroxismal pain aggravation during follow-up, VAS score</td>
<td>3.2±1.6</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Decrease in the need for medication during follow-up, VAS score</td>
<td>3.1±1.5</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Decrease in the impact of pain during follow-up (VAS score) on:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>general condition</td>
<td>4.1±1.7</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>mood</td>
<td>4.5±1.2</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>attitude to others</td>
<td>3.4±1.4</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>daily activity</td>
<td>3.5±1.1</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>passive recreation</td>
<td>3.1±1.5</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>self-care</td>
<td>3.7±1.0</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>sleep</td>
<td>3.5±1.3</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>sexual activity</td>
<td>2.8±2.0</td>
<td>(p&lt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>

The introduction of motor cortex stimulation to treatment of neuropathic pain are now argued. For example, an initially supposed direct correlation between the degree of motor function preservation and the efficacy of motor cortex stimulation [19, 20] was disproved later [15, 21]. The TMS efficacy is not clearly recognized as a reliable prognostic factor [14, 21]. Recent studies have shown that this criterion has a high reliability (according to various data, 79 to 90%) in predicting the positive result of epidural cortical stimulation and a significantly lower reliability (35 to 67%) in predicting the negative result of MCS [16, 22]. Earlier publications also considered a regression of pain in response to thiopental [23] and ketamine [24] administration as a predictor of the motor cortex stimulation efficacy; however, these criteria were not put into widespread practice.

**Fig. 4. The mean profile of pain and quality of life for patients in the short-term (a) and long-term (b) follow-up.**

The external outline is a condition before surgery, the internal outline is a condition after surgery.

A — maximum pain intensity; B — minimum pain intensity; C — rate of pain episodes; D — mean pain intensity; E — need for analgesics; F–M — effect of pain on the overall health (F), mood (G), motor activity (H), passive recreation (I), self-care (J), attitude to others (K), sleep (L), and sexual activity (M).
In not all cases of the present study, we were able to find a direct relationship between the motor function preservation or TMS efficacy and the result of chronic motor cortex stimulation; however, this correlation was present in most cases. The state of motor function and the results of transcranial magnetic stimulation and epidural cortical stimulation during follow-up are presented in Table 4.

All patients were admitted to implantation of cortical electrodes based on positive results of repetitive transcranial magnetic stimulation. For example, a patient 3 with flaccid peripheral paresis of the right arm, worsening to plegia in the distal arm, noted a good and relatively stable analgesic effect associated with chronic ES. In the same patient, we also observed a distinct analgesic effect of TMS that lasted several hours.

A patient 7 with central tetraparesis after a spinal cord injury at the cervical level had a positive result of TMS; a good effect of stimulation lasted for 3 years, and not only pain but also spasticity regressed. A further reduction in the analgesic effect of ES was accompanied by a parallel increase in the spasticity regressed. AMT, 50 µg/day; GBP, 900 µg/day; TRM, 1.0 up to 4—6 times per day

<table>
<thead>
<tr>
<th>№</th>
<th>Pain history, years</th>
<th>Onset of treatment, years</th>
<th>Treatment before stimulation</th>
<th>Treatment in association with stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>3</td>
<td>AMT, 50 µg/day; GBP, 900 µg/day; TRM, 1.0 up to 4—6 times per day</td>
<td>MPT, 37.5 µg/day; CLZ, 1.0 µg/day; CBZ, 600 µg/day; TRM, 1.0 once a day</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>CBZ, 1,200 µg/day</td>
<td>CLZ, 2.0 µg/day; CBZ, 600 µg/day</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>AMT, 75 µg/day; GBP, 900 µg/day; TRD, 1.0 up to 4—6 µg/day</td>
<td>GBP, 600 µg/day; CLZ, 1.0 µg/day; TRD — dr</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0</td>
<td>AMT, 75 µg/day; GBP, 900 µg/day; DZP, 10 µg + CP, 100 µg once a day; TRD, up to 400 µg/day</td>
<td>GBP, 600 µg/day; HXZ, 25 µg/day; TRD, 1.0 once a day</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>NSAIDs and TRD, up to 4 times per day. Initially, the patient refused analgesics; later: AMT, 30 µg/day; CLZ, 1.0 µg/day</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
<td>CBZ, 1,200 µg/day</td>
<td>CBZ, 600 µg/day; GBP, 900 µg/day</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>0</td>
<td>TZD, 24 µg/day; CTD, 600 µg/day; TRD, 150 µg/day</td>
<td>CBZ, 300 µg/day; PRX, 20 µg/day. Doses of CTD, TRD, and TZD</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2</td>
<td>GBP, 1,800 µg/day; CLZ, 2.0 µg/day; TRD, 400 µg/day</td>
<td>GBP, up to 900 µg/day; CLZ, 1.0 µg/day; TRD — dr</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>0</td>
<td>CBZ, 600 µg/day; AMT, 75 µg/day; GBP, 1,800 µg/day; TRD, up to 1 g/day</td>
<td>AMT, GBP, and TRD — dr. CBZ, 600 µg/day; CLZ, 1.0 µg/day</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0</td>
<td>CBZ, up to 1,400 µg/day; GBP, up to 1,800 µg/day; DLX, up to 60 µg/day; TRD, up to 600 µg/day</td>
<td>TRD — dr. GBP, up to 900 µg/day; CLZ, 1.5 µg/day</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>3</td>
<td>PGB, up to 600 µg/day; AMT, 75 µg/day; CLZ, 2.0 µg/day; TRD, i/m, up to 4 times per day</td>
<td>CLZ, 2.0 µg/day; PGB, up to 300 µg/day; AMT, up to 50 µg/day; TRD — dr</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>3</td>
<td>GBP, up to 1,800 µg/day; TRD, tabs and i/m, up to 8 times per day; AMT, up to 150 µg/day</td>
<td>GBP, up to 900 µg/day; TRD, up to 400 µg/day; AMT, up to 75 µg/day</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>1</td>
<td>CBZ, up to 600 µg/day; CTP, 10 µg/day; CLZ, 2.0 µg/day; ANF, 50 µg/day; PGB, 600 µg/day; TRD, PGB, up to 600 µg/day</td>
<td>PGB, up to 450 µg/day; ANF, 50 µg/day; TRD — dr</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>0.5</td>
<td>TRD, up to 400 µg/day; CBZ, 600 µg/day; AMT, 75 µg/day; narcotic analgesics</td>
<td>GBP, 900 µg/day; AMT, 75 µg/day; TRD, 1.0 i/m, up to 2 times per day; narcotic analgesics — dr</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>2</td>
<td>GBP, up to 1,800 µg/day; AMT, 75 µg/day; TRD, i/m, up to 4 times per day</td>
<td>GBP, up to 900 µg/day; AMT, 59 µg/day; TRD, 0.01 up to 2 times per day</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
<td>2</td>
<td>AMT, 50 µg/day; PGB, up to 600 µg/day; CBZ, up to 600 µg/day; TRD, i/m, up to 10 times per day; BTP, i/m, up to 10 times per day</td>
<td>PGB, up to 300 µg/day; AMT, 75 µg/day; CLZ, 1.0 µg/day; TRD, 1.0 i/m, 1—2 times per day</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>10</td>
<td>TRD, KTR, MRP. During last 2 years: CBZ, 1,200 µg/day; AMT, 75 µg/day</td>
<td>In the period of effective stimulation: TRD, 1.0 i/m, up to 3 times per day; CBZ, up to 1,000 µg/day; AMT, 75 µg/day</td>
</tr>
<tr>
<td>18</td>
<td>4</td>
<td>0</td>
<td>CBZ, 1,000 µg/day; PGB, 600 µg/day</td>
<td>Refusal of medications</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>2</td>
<td>CLZ, up to 2.0 µg/day; PGB, up to 600 µg/day; no AMT</td>
<td>AMT, up to 50 µg/day; CLZ, up to 2.0 µg/day</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>2</td>
<td>AMT, 75 µg/day; GBP, up to 1,800 µg/day</td>
<td>In the period of effective stimulation: ANF, 75 µg/day; GBP, up to 600 µg/day</td>
</tr>
</tbody>
</table>

neurotization level on the background of dramatic events in the patient family life. It should also be noted that the antispasmodic effect of ES, in contrast to the analgesic effect, remained stable. In a patient 6 without motor dysfunction and with a positive result of TMS, the stimulation efficacy vanished in the test period. It is noteworthy that another, more significant prognostic factor — the intensity of a psychogenic pain component that we were not able to identify before test stimulation, prevailed in this case. A patient 12 with severe psychogenic pain in the left limbs noted significant pain relief associated with stimulation for a long time, until the development of a complication (see above), so he was able to work. Most likely, the absence of the limb in the case of phantom pain and the lack or gross limitation of movements in the “formally” existing limb are not prognostically equivalent. This is indicated by both the positive results of chronic ES of the motor cortex in the case of phantom limb pain, which are described in the current literature, and the positive results in all patients with phantom limb pain in our small series. With all things being equal, the intensity of a psychogenic pain component and a high neurotization level are the key predictor for motor cortex ES in particular and for any of the neurostimulation techniques in general.

Apparently, some uncertainty of the patient selection criteria and predictors for the efficacy of motor cortex stimulation in the treatment of chronic pain syndromes is associated with the fact that the mechanisms of cortical stimulation still remain unclear [14, 25]. Today, the prevailing theory is activation of structures of the antinociceptive system [14, 25, 26]. In recent animal studies [28, 30, 31, 39], it was hypothesized that a prolonged analgesic effect of MCS may be due to activation of the descending antinociceptive system, including periaqueductal gray matter, as well as activation-associated changes in protein synthesis and increased secretion of inflammatory mediators at the segmental level. N. Reynolds et

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Age, years</th>
<th>Pain history, years</th>
<th>Motor function</th>
<th>TMS outcome: pain regression level (VAS score and duration)</th>
<th>Outcome of epidural cortical stimulation during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>42</td>
<td>8</td>
<td>Peripheral monoparesis, up to 2—3 points</td>
<td>&gt;50%, &gt;1 h</td>
<td>Negative effect after 10 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>64</td>
<td>3</td>
<td>No paresis</td>
<td>70%, several hours</td>
<td>Positive. The patient died after 3 years</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>45</td>
<td>2</td>
<td>Peripheral monoparesis of the right arm, up to 3 points in the proximal arm and up to plegia in the distal arm</td>
<td>Not less than 30%, several hours</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>3</td>
<td>Peripheral monoparesis of the left arm, up to 3 points, and central monoparesis of the left leg, up to 4 points</td>
<td>&gt;50%, 2 days</td>
<td>Positive</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>42</td>
<td>2</td>
<td>Monoplegia of the left arm</td>
<td>Not less than 30%, several hours</td>
<td>Positive</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>39</td>
<td>2</td>
<td>No pareses</td>
<td>Less than 30%, up to 1 hour</td>
<td>Negative test stimulation</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>54</td>
<td>7</td>
<td>Spastic tetraparesis, up to 1—2 points, in the distal parts and up to 3 points in the proximal parts</td>
<td>Pain regression by 50% (VAS); spasticity regression by 2 points (Ashworth); few hours</td>
<td>Stimulation effect disappeared after 3 years</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>42</td>
<td>7</td>
<td>Peripheral monoparesis of the right arm, up to 3 points</td>
<td>&gt;50%, several hours</td>
<td>Positive. Communication with the patient was lost</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>26</td>
<td>8</td>
<td>No paresis</td>
<td>&gt;50%, 3 h</td>
<td>Positive</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>50</td>
<td>2</td>
<td>No paresis</td>
<td>90%, several hours</td>
<td>Positive</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>51</td>
<td>6</td>
<td>No apparent paresis</td>
<td>&gt;30%, 1 h</td>
<td>Positive</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>46</td>
<td>6</td>
<td>Functional stumps. No paresis</td>
<td>&gt;70%, 6 h</td>
<td>A system was removed due to complications</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>61</td>
<td>2</td>
<td>Left-sided central hemipares, up to 4 points</td>
<td>&gt;50%, 2 h</td>
<td>Positive</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>46</td>
<td>2</td>
<td>Peripheral monoparesis of the right arm, up to 2—3 points</td>
<td>&gt;50%, 2 h</td>
<td>Positive</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>59</td>
<td>5</td>
<td>Left-sided central hemipares, up to 4 points</td>
<td>&gt;50%, 1 day</td>
<td>Positive</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>60</td>
<td>7</td>
<td>A stump is functional</td>
<td>&gt;50%, 1 h</td>
<td>Positive</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>60</td>
<td>12</td>
<td>Peripheral monoparesis of the right arm, up to 4 points in the proximal arm and up to plegia in the distal arm</td>
<td>&gt;50%, 1 h</td>
<td>Negative effect after 5 months</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>73</td>
<td>4</td>
<td>No paresis</td>
<td>90%, 1 day</td>
<td>Positive</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>59</td>
<td>2</td>
<td>No paresis</td>
<td>&gt;50%, 1 day</td>
<td>Positive</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>74</td>
<td>6</td>
<td>Central left-sided hemiparesis, up to 4 points in the arm and up to 3 points in the leg</td>
<td>30%, 30 min</td>
<td>Positive. A stimulator was removed because of complications</td>
</tr>
</tbody>
</table>

Table 4. Motor function and outcomes of transcranial magnetic stimulation and epidural cortical stimulation during follow-up
al. [32] demonstrated that motor cortex stimulation affects the beta rhythm changes characteristic of neuropathic pain.

Therefore, despite the common view on the mechanism of motor cortex stimulation in general, more detailed neurophysiological and neurobiochemical effects underlying the mechanism still remain poorly understood.

Conclusion

Chronic epidural ES of the motor cortex is an effective treatment for a variety of severe drug-resistant neurogenic pain syndromes. If the effect reduces during the follow-up period, it can be restored by a periodic variation of the ES parameters.

The positive result of transcranial magnetic stimulation may be a predictor of a good result of chronic motor cortex stimulation, but implantation of the entire system for stimulation is advisable to perform after a test period of 10—14 days. A pronounced psychogenic component in the chronic pain picture and a high neurotization level are predictors of a negative result of chronic neurostimulation in the case of long-term follow-up.

Enhancing the MCS efficacy can be achieved by repeated re-programming of a system, improvement of neurostimulators and electrodes, and clarification of ideas about the mechanisms of motor cortex stimulation and the principles of patient selection. Further research is needed to clarify the criteria for patient selection and predictors of the long-term efficacy of MCS in the treatment of neuropathic pain syndromes.

Authors declare no conflict of interest.

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Commentary

The review of clinical experience with motor cortex stimulation for treatment of refractory chronic neuropathic pain syndromes is of great interest, and I would congratulate the authors for the excellent results and a detailed analysis of the clinical data.

The presented study is one of the world’s largest trials conducted at a single institution. Since the introduction of motor cortex stimulation in the treatment of various neuropathic pain syndromes, researchers and clinicians at various medical centers have tried to establish criteria for selection of ideal candidates for surgery as well as predictors of successful outcomes. But so far, all these attempts have not led to the development of a comprehensive and universal protocol. This fact partly explains why motor cortex stimulation has not become a widespread treatment for pain and has not received official approval in many countries.

In this situation, the authors’ experience is even more valuable. In addition to the most understandable presentation of the literature, the authors collected comprehensive clinical material and compared related series of carefully selected patients who were examined and eventually treated by motor cortex stimulation. The authors analyzed the results of stimulation based on the baseline pain intensity level as well as other factors, such as age, gender, disease duration, results of various clinical and psychological tests, and also results of preoperative test transcranial magnetic stimulation of the cerebral cortex.

In addition to the most understandable presentation of the authors’ approach to selection of patients and the detailed description of the surgical technique, the article presents a detailed and very informative description of follow-up in all patients. This detailed information deserves publishing in a peer-reviewed journal to make these data available to other researchers for further analysis.

One of the most important findings in the presented study is the safety of the technique that was confirmed by the lowest possible complication rate and the lack of any serious negative impact on the quality of life of operated patients. This gratifying fact certainly encourages us to recommend using motor cortex stimulation in cases where other treatments do not lead to a significant decrease in the pain intensity.

The treatment success rate varied depending on the individual features of patients, and I agree with the authors that it is impossible to make comprehensive conclusions in the case of a small number of patients in each diagnostic group. However, I support the authors’ conclusions on the satisfactory efficacy and safety of motor cortex stimulation. On the basis of my own experience, I continue to use this treatment for some specific indications. In my practice, motor cortex stimulation is used only in patients with post-stroke central deafferentation pain syndromes as well as with facial anesthesia dolorosa after surgery for the trigeminal nerve.

In our practice, we use MRI to localize the motor cortex and integrate the obtained data into a navigation system. We identify the stimulation target by neurophysiological monitoring. Our surgical approach involving high field MRI was presented in a previously published paper [1]. Actually, motor cortex stimulation was indicated in our previously published algorithm for facial pain treatment [2, 3].

I think the most important conclusion of this work is that preoperative transcranial magnetic stimulation is not a predictor for the efficacy of motor cortex stimulation — this problem was previously discussed in the literature. Also, I agree with the authors’ idea that preservation of the motor function is not a prerequisite for achieving a significant clinical improvement in patients with motor cortex stimulation.

However, I would like to add to the authors’ presentation that, although motor cortex stimulation works even in the absence of movements in the affected part of the body, but preservation of the motor cortex is required. According to our experience, motor cortex stimulation is not effective in patients with central post-stroke pain syndromes in whom the motor pathways were not initially damaged by stroke as well as in patients in whom we were unable to localize the motor cortex using preoperative functional MRI.

Konstantin V. Slavin, Professor, Head of the Section of Stereotactic and Functional Neurosurgery, University of Illinois at Chicago, USA

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Objective. Chiari malformation is characterized by herniation of the cerebellar tonsils into the foramen magnum, which leads to disturbance of CSF circulation through the craniovertebral junction. Orthostatic stress, which makes CSF flow through the cranio-vertebral junction, is an adequate method to detect these disorders. It is accompanied by changes in intracranial pressure, affecting the cerebrovenous orthostatic reactivity (CVOR), which is non-invasively assessed in patients with Chiari malformation. Material and Methods. The study involved 35 patients with Chiari malformation (26 patients with Chiari I and 9 patients with Chiari II malformation) aged 4 to 58 years. Hydrocephalus and syringomyelia was diagnosed in 4 and 6 examined patients, respectively. Transcranial Doppler sonography was used to record the venous blood flow in the straight sinus of the brain while changing body position on the tilt table from +90° to –30°. Results. There is significant CVOR abnormality in most patients with Chiari malformation (more than 90%), which is characterized by either increased CVOR (sometimes 5—6-fold compared to the upper normal level (considerable hyperreactivity)) or complete absence of any changes during orthostatic load (nonreactivity). Before surgical treatment, CVOR of patients with Chiari malformation is often characterized by nonreactivity, as well as a moderate or significant hyperreactivity. After surgical treatment (foramen magnum decompression), patients with Chiari malformation demonstrate significant normalization of the craniovertebral volume ratios and CVOR is often characterized by normoreactivity (in 63%) or, more rarely, moderate hyperreactivity. The venous flow velocity in the straight sinus of the brain in patients with Chiari malformation can be increased before the surgery and is normalized after surgery. Conclusions. The high incidence of disturbance of CVOR (over 90%) was revealed in patients with Chiari malformation. After surgical treatment, CVOR was completely normalized in more than half of these patients (63%).

Keywords: venous brain circulation, craniovertebral junction, Chiari malformation.

Abbreviations
ICP — intracranial pressure;
CVVRs — craniovertebral volume ratios;
CVJ — craniovertebral junction;
CM — Chiari malformation;
VBFV — venous blood flow velocity;
TCD — transcranial Dopper (sonography);
CVOR — cerebrovenous orthostatic reactivity.
in compliance of the cerebrospinal system and, therefore, increase its elastance [5]. Meanwhile, the opposite effect (significantly increased brain compliance and reduced elastance) is the main result of surgical decompression of CVJ in patients with CM. These changes can be caused by normalization of the CSF flow through the CVJ in patients with CM. Meanwhile, the changes in the degree to which the brain structures are displaced are much smaller after surgical decompression of the foramen magnum compared to the increase in compliance of the cerebrospinal system [5]. Hence, the nonfocal factors (changes in the viscoelastic properties of the cerebrospinal system) are much more specific for CM than the local changes in the CSF flow velocity through the CVJ. CM is known to be an inherited disorder. However, the clinical manifestations of CM tend to occur in adulthood. N. Alperin et al. [5] believe that such a late manifestation of the clinical signs of CM is because brain elastance gradually increases with age [6]. A non-invasive ultrasound method that allows one to assess the viscoelasticity of the cerebrospinal system, as well as venous brain circulation and the CSF dynamics, has been developed at the N.N. Burdenko Neurosurgical Institute [7, 8].

The aim of the present study was to use this method to investigate the viscoelastic properties of the cerebrospinal system, CSF dynamics, and cerebral venous flow in patients with CM.

Clinical material

The study involved 35 patients with CM (Chiari I – 26 patients, Chiari II – 9 patients) aged 4 to 58 years. Four of the examined patients had hydrocephalus; six patients had syringomyelia. The most frequent complaints included neck pain, severe headache that was made worse by sneezing or coughing; swallowing disturbance; sensory and motor disorders, such as numbness of the limbs and ataxia. The average size of herniation of cerebellar tonsils into the foramen magnum was 8.2±3.1 mm. No correlation between the degree of herniation into the foramen magnum and the severity of neurological symptoms was found.

The procedure of our own studies

According to the Monro—Kellie doctrine [9, 10], the major intracranial volumes of the cerebral tissue, blood, and CSF are normal. One of these volumes can be changed only if the volumes of other components of intracranial contents are altered correspondingly. The normal volumes of the cerebral tissue is 1100—1300 cm3; CSF, 130—150 cm3; and blood, 60—80 cm3 [11]. Stability of the cerebral hemodynamics is ensured by functioning of the complex, multi-component cerebral blood flow regulation system [12—14]. In addition to quantification of each intracranial volume (cerebral tissue, blood, and CSF), the total characteristics of the craniovertebral volume ratio (CVVR) that is determined as the tightness of the entire cerebrospinal system [15—17] is also crucial. For this purpose, the dependence between the additional volume in the CSF space and the resulting changes in intracranial pressure (ICP) is studied. Sterile normal saline injected intralumbarly is usually used as the additional solution; the changes in ICP can be assessed simultaneously [15—18]. Unfortunately, the invasiveness of this method significantly limits its clinical use. The changes in CVVRs occur under natural physiological conditions. When the vertical body position is changed to the antioorthostatic position, CSF partially migrates from the spinal CSF space into the intracranial CSF space. This natural, non-invasive, intracranial infusion of CSF through the CVJ increases the intracranial volume of CSF and ICP. Under these conditions, bridging veins running in the subarachnoid space are compressed in a cuff-like manner, which is accompanied by weaker venous outflow through the deep cerebral veins and the straight sinus [19]. Hence, it is no wonder that there is a good correlation between the ICP measured using a catheter inserted into the ventricular system and blood flow in the straight sinus recorded by Transcranial Dopper (TCD) sonography [20], which allows one to non-invasively assess ICP. ICP can be measured non-invasively by varying the patient’s body position on a tilt table [21]. Transcranial Doppler registration of venous blood flow in the straight sinus under orthostatic stress is an adequate method for assessing the CVVRs and allows one to assess the hemodynamic status [8, 22]. We studied the changes in the velocity of systolic venous blood flow flow in the straight sinus and the amplitudes of venous blood flow pulse vibrations under orthostatic load both in healthy volunteers (Fig. 1) and in patients with pathology. To non-invasively study venous blood flow velocity (VBVF) in the straight sinus by TCD, we placed an ultrasound sensor on the cranial surface near the external occipital protuberance. The straight sinus was located at a depth of 55 mm. CVOR was studied in 45 healthy individuals aged 2 to 82 years. Fig. 1 shows the orthostatic profile of venous circulation in a healthy woman.

Fig. 1 demonstrates that VBVF in the straight sinus remains stable in a wide range of changes in body position on the tilt table (from +90° to 0°). Meanwhile, VBVF in the straight sinus gradually increases in the range of angles between 0° and −30°. The reason for these changes in venous blood flow may lie behind postural fluctuations in intracranial pressure that is based on redistribution of CSF within the cerebral and spinal CSF spaces. When using a similar functional load (changes in body position on the tilt table within the range from +90° to −30°) in 7 patients operated on for brain tumors, with their ventricular pressure continuously measured using implanted telemetric sensors, we have also revealed two areas where ventricular pressure was stable and gradually increased [21]. The stable pressure area was typically located in the range from +25°, +35°, up to +90°, while the increasing pressure area corresponded to the range of
orthostatic load from $-25^\circ$ to $+30^\circ$; the dependence between the body tilt angle and an increase in ventricular pressure approached the linear one. Both the experimental [23] and clinical [15] studies showed the presence of two areas corresponding to stable and increasing ICP as the additional intracranial volume was increased. The stable pressure area characterizes the intracranial spatial compensation (the reserve capacity), while the increasing pressure zone characterizes elastic compensation (elastance gradient).

In our studies, systolic flow velocity in the straight sinus was registered by TCD sonography as the body position on the tilt table was gradually changed from $+90^\circ$ to $-30^\circ$. The dependence between systolic flow velocity and body position is characterized by two straight lines: 1) the spatial compensation area, where systolic flow velocity is stable and 2) the elastance compensation area, where systolic flow velocity gradually increases. The tilt angle of this line characterizes the elastance of the craniovertebral contents, while the intercept point of these two lines characterizes its reserve capacity. VBFV is stable in the spatial compensation area and characterizes the state of cerebral venous circulation. As a result of our studies, we detected the group of patients with VBFV in the straight sinus remaining stable (nonreactivity) as their body position on the tilt table was varied within the entire range, from the orthostatic position ($+90^\circ$) to antioethostatic position ($-30^\circ$). Meanwhile, in other patients, VBFV in the straight sinus increased to different extents as their body position on the tilt table was changed in the same range of angles. Taking these data into account, the term “cerebrovenous orthostatic reactivity” is the most adequate term characterizing changes in venous blood flow under orthostatic functional load. To quantify CVOR, the degree to which VBFV in the straight sinus increased (cm/s) is divided by the entire range of variation of body position on the tilt table (degrees) within which VBFV in the straight sinus was increasing. The major quantitative characteristics of CVVR in healthy individuals were appreciably stable, while the range of their fluctuations was reported in the clinical protocol (Table). Table lists the results of studying the cerebral venous circulation, the CSF dynamics, and craniovertebral volume ratios in healthy individuals.

The data listed in Table demonstrates that the reserve capacity of CVVR in healthy individuals ranges between 0° and $+15^\circ$; the velocity of systolic venous flow in the spatial compensation area (VBFV) varies between 14 and 28 cm/s; the amplitude of pulse vibrations of the venous flow in the same zone (AMP) in the norm ranges from 6 to 8 cm/s; and cerebrovenous orthostatic reactivity (CVOR) ranges from 0.15 to 0.35 cm/s/°. The CSF dynamics is assessed according to the time required for the velocity of venous blood flow to become stable again as the tilt table position is changed from the horizontal to the vertical one (no more than 5 s in the norm).

All the results were processed statistically. The method was found to be highly reproducible when comparing the results of repeated studies for the same person. The data listed in Table demonstrate that CVOR is stable and varies within a small range in healthy individuals.

Meanwhile, when the craniovertebral volume ratios were varied to different extents, the CVOR significantly differed from the norm: it could both increase (sometimes 5—6-fold compared to the upper limit of the norm — significant hyperreactivity) and substantially decrease (up to complete absence of any changes in venous blood flow in the straight sinus under orthostatic load — nonreactivity). Different patients had different degrees of changes in CVOR (nonreactivity, hyporeactivity, normoreactivity, moderate or significant hyperreactivity).

The quantitative characteristics of changes in cerebrovenous orthostatic reactivity (CVOR cm/s/°) are represented as follows.

Fig. 2 shows different types of cerebrovenous orthostatic reactivity (CVOR).

One of the variants of CVOR is nonreactivity (upper curve in Fig. 2), which is characterized by no changes in VBFV in the straight sinus within the entire range of body positions on the tilt table (from $-30^\circ$ to $+90^\circ$).

Results

Among the examined 35 patients with CM, only 3 (9%) patients had no changes in CVOR before the surgery. In the remaining 32 cases, various types of CVOR disorders were preoperatively observed (nonreactivity, moderate or significant hyperreactivity). Meanwhile, CVOR was completely normalized after surgical management in more than half cases (63%), while the remaining patients had moderate cerebrovenous orthostatic hyperreactivity.

Cerebrovenous orthostatic nonreactivity was preoperatively observed in 14 patients with CM. The same patients had increased VBFV in the straight sinus.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Y axis shows the orthostatic profile of venous cerebral circulation in a healthy 34-year-old woman (estimation based on systolic flow velocity). X axis shows variation of body position on a tilt table.}
\end{figure}
The results of examination of a 37-year-old woman with CM can be used as an example of cerebrovenous orthostatic nonreactivity accompanied by increased VBFV and normalized CVOR after surgical decompression of the foramen magnum. Six years ago after a traumatic brain injury (falling from her own height and hitting the back of her head while remaining conscious) the patient started to have head and neck pain, which later was gradually aggravated. One year after the pain syndrome had emerged, MRI showed CM (invagination of cerebellar tonsils into the foramen magnum 8 mm below the Chamberlain—Chiari II line). The patient permanently received conservative therapy; however, neck pain was gradually aggravated, especially after another head injury one year later (a downward shock into the occipital region). A year ago the patient started to feel occasional numbness in the left hand. One of the headache attacks was accompanied by severe vertigo and loss of consciousness. Repeated MRI exam showed the more significant downward displacement of the cerebellar tonsils by 13 mm below the Chamberlain line. Neurological examination showed pain in the occipital area, mild symptoms affecting the brain stem and cerebellum presented as gaze-evoked nystagmus on lateral gaze, instability when performing Romberg’s test, and transient hypoesthesia in the C5—C7 units on the left side.

The patient was subjected to C1 laminectomy and craniovertebral junction decompression. The early postoperative period was uncomplicated; regression of neurological symptoms included alleviation of neck pain and headache, elimination of sensory disorders and brain stem—cerebellar symptoms.

Fig. 3 shows the results of examining the patient.

Before surgery, the patient had cerebrovenous orthostatic nonreactivity, which can be attributed to blockage of CSF flow through the craniovertebral junction. In addition, venous flow velocity in the straight sinus was preoperatively increased (45 cm/s) due to increased ICP. After the surgery, venous flow in the straight sinus and CVOR were normalized (venous flow velocity decreased to 20 cm/s; CVOR corresponded to orthostatic normoreactivity — 0.33 cm/s/°), which can indicate that the ICP had normalized and the normal CSF flow through the craniovertebral junction had recovered.

Patients with CM typically had cerebrovenous orthostatic hyperreactivity before surgery (18 cases). After surgical management, the CVOR in this group of patients decreased to normoreactivity.

Assessment of the preoperative distribution of CVOR most frequently showed cerebrovenous orthostatic nonreactivity and moderate hyperreactivity. Meanwhile, normoreactivity and significant hyperreactivity were detected much less often. In the same group of patients, cerebrovenous orthostatic hyporeactivity was not detected at all before the surgery (Fig. 4, left-hand side).

The CVVR values in patients with CM significantly changed after surgical management: cerebrovenous orthostatic normoreactivity and, less frequently, moderate hyperreactivity were detected in most patients (Fig. 4, right-hand side). Patients after surgery showed neither cerebrovenous orthostatic nonreactivity nor significant hyperreactivity, although these conditions took place before surgery. Cerebrovenous orthostatic nonreactivity in patients with CM was accompanied by the increased mean SFV values in the straight sinus reaching –32.6 cm/s (normal value, –24.3 cm/s); the difference between the venous flow velocity in patients with CM and the normal value was statistically significant (p<0.004). Surgical management resulted in a statistically significant decrease in the SFV in the straight sinus (p=0.003).

Discussion

The CVJ plays a crucial role in interaction between the CSF systems in the brain and spinal cord. CVJ pathologies may change this interaction and cause imbalance in the CSF dynamics and cerebral venous circulation. Investigation of these disorders contributes to elucidating the degree to which the CVJ is obstructed, which may have diagnostic value when determining the indications for surgical management and for evaluating its effectiveness.

It has been found that a change in the body position of a healthy individual causes significant variations in ICP: it decreases in the orthostatic (vertical) position and increases in the horizontal or antioorthostatic (head below horizontal) position [21]. Migration of CSF through the CVJ can be one of the reasons for postural fluctuations in ICP when changing body position. Gravitational effects under the same orthostatic load may cause migration of CSF through the CVJ in different directions: in the caudal direction in orthostatic position

Cerebral venous circulation, CSF dynamics, and craniovertebral volume ratios. Examination protocol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic flow velocity (SFV) in the straight sinus in horizontal position, cm/s</td>
<td>14—28</td>
</tr>
<tr>
<td>Pulse amplitude (AMP) in the straight sinus in horizontal position, cm/s</td>
<td>6—8</td>
</tr>
<tr>
<td>Systolic blood flow (SFBFV) in the straight sinus in the spatial compensation area, cm/s</td>
<td>14—28</td>
</tr>
<tr>
<td>Pulse amplitude (AMP) in the straight sinus in the spatial compensation area, cm/s</td>
<td>6—8</td>
</tr>
<tr>
<td>CSF dynamics</td>
<td>No more than 5 s</td>
</tr>
<tr>
<td>Cerebrovenous orthostatic reactivity (CVOR), cm/s/°</td>
<td>0.15—0.35</td>
</tr>
<tr>
<td>Reserve capacity, °</td>
<td>0 (+15)</td>
</tr>
</tbody>
</table>
and in the oral direction in antiorthostatic position. Hence, applying an orthostatic load is an adequate method for assessing passability of the CVJ as it detects blockage of the CVJ and different degrees of its stenosis. The role of gravitational effects on the CVVR values and cerebral venous circulation is especially noticeable in a zero-gravity environment during space flights [25]. Different conditions of venous blood outflow from the cranial cavity may also play a role for postural fluctuations in ICP. In horizontal position, venous blood flows out of the skull mostly via the jugular veins, while in vertical position it flows via the vertebral plexus veins [25, 26, 28]. The volume flow rate of venous blood via the internal jugular veins in vertical position is 70 mL/min, while increasing tenfold to reach 700 mL/min in horizontal position [26]. Compliance of the cerebrovascular system increases significantly (2.8-fold) in the vertical position; hence, its elastance decreases [27]. Meanwhile, ICP and cerebral elastance depend exponentially on the volume of intracranial contents [18]. The intracranial volume of blood and CSF decreases in the vertical position, thus reducing ICP [28]. Pathology of the CVJ may change the CSF dynamics and conditions of venous blood outflow from the cranial cavity.

We have detected to main types of changes in CVOR in patients with CM: nonreactivity and hyperreactivity (either moderate or significant). Cerebrovenous orthostatic nonreactivity in pathology of the CVJ is most likely to be caused by blockage of CSF flow between the subarachnoid space of the brain and spinal cord. Disintegration of the cerebral and spinal CSF space seems to be the main reason for syringomyelia in patients with Chiari malformation [28—30]. Furthermore, herniation of cerebellar tonsils into the foramen magnum causes compression of the internal vertebral venous plexus located extradurally. It disturbs redistribution of venous blood outflow from the skull under orthostatic load, which may also contribute to development of cerebrovenous orthostatic nonreactivity. In a healthy person under antiorthostatic conditions, CSF partially migrates from the spinal CSF space into the cerebral one, resulting in an increase in ICP. The strong correlation between ICP and SFV in the CVJ [20] may be the reason for increasing SFV in the CVJ under antiorthostatic conditions. The absence of an increase in SFV in the CVJ under antiorthostatic conditions and development of cerebrovenous orthostatic nonreactivity may attest to blockage of the CVJ and disintegration of the CSF space in the brain and spinal cord in patients with CM. Registration of ICP under orthostatic load using ICP sensors located extradurally is an adequate method for assessing the passability of the CVJ. The use of this method in patients with CM made it possible to detect the statistically significant weakening of postural fluctuations in ICP, which attested to disruption of passability of the CVJ [31]. However, the invasiveness of this method substantially limits its clinical use. Not only cerebrovenous orthostatic nonreactivity was detected in patients with CM but also hyperreactivity, which was most likely caused by obstruction of CSF flow through the CVJ, resulting in increased ICP and elastance of CVVR. Increased elastance (decreased compliance of the brain) in patients with CM was also detected by N. Alperin et al. [5] who used modified MRI. After surgical management (decompression of the foramen magnum), the examined patients had significantly normalized CVVR values, while CVOR was typically characterized by normoreactivity or, less frequently, by moderate hyperreactivity. No cases of cerebrovenous orthostatic nonreactivity that is typical of blockage of the CVJ were detected after surgical management of patients with CM.

Surgical decompression of the CVJ resulted in either partial or complete normalization of CVOR after nonreactivity detected before the surgery. In patients who preoperatively had cerebrovenous orthostatic hyperreactivity, the degree of hyperreactivity always decreased (usually to normal values) after surgical management. According to the data obtained by N. Alperin et al. [5] using modified MRI, a significant increase in compliance of the brain (and, therefore, a decrease in its elastance) is the main effect of surgical decompression of the CVJ in patients with CM. These changes can result from normalization of CSF flow.
through the CVJ. In patients with CM, changes in the degree of displacement of cerebral structures and CSF flow velocity through the CVJ after surgical decompression are much less pronounced than the increase in compliance of the craniovertebral contents.

The main result of the studies is that the high occurrence of CVOR disorders (over 90%) in patients with CM has been detected. Meanwhile, more than half of these patients (63%) show total normalization of CVOR after surgical management, while the remaining patients show a statistically significant decrease in the degree of pathology. Surgical management completely eliminates cerebrovenous orthostatic nonreactivity (being indicative of blockage of the CVJ) and statistically reliably reduces the degree of hyperreactivity that is typical of CVJ stenosis. These data demonstrate that CVOR has a high diagnostic significance for assessing the passability of the CVJ.

The preoperative changes in CVOR (nonreactivity, hyperreactivity) and its normalization after surgical management were observed not only in patients with CM but also in individuals having tumors in the CVJ [32] and invagination of the odontoid process of the C2 vertebra [33], which may indicate that they depend on disturbance of CSF dynamics and hemodynamics in the CVJ rather than on the features of different clinical entities. Blockage of the CVJ is characterized by cerebrovenous orthostatic nonreactivity, which was usually combined with statistically significant increase in SFV in the CVJ (up to 80 cm/s) compared to that in the control group of healthy

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**Fig. 3. Results of examining the 37-year-old patient with Chiari malformation.**

a — Preoperative MRI scan of the brain shows that cerebellar tonsils displaced downward, into the foramen magnum; b — study of cerebrovenous orthostatic reactivity (right top corner — before surgery; right bottom corner — after surgery).

**Fig. 4. Occurrence of different degrees of changes in cerebrovenous orthostatic reactivity (CVOR) in patients with Chiari malformation before (left-hand side) and after (right-hand side) surgery.**

Y axis represents the different degrees of changes in CVOR (nonreactivity, hyporeactivity, normoreactivity, moderate hyperreactivity, and significant hyperreactivity). X axis shows the number of cases.
volunteers; SFV in the CVJ is typically normalized after surgical management. Taking into account the strong correlation between SFV in the CVJ and ICP [20], we can suggest that the twofold increase in the mean SFV values compared to the norm may be caused by intracranial hypertension.

Cerebrovenous orthostatic nonreactivity was also observed in patients with idiopathic normal pressure hydrocephalus [22]; however, it was characterized by the significantly reduced SFV in the CVJ (up to 10 cm/s) for this clinical entity. Cerebrovenous orthostatic nonreactivity in patients with idiopathic normal pressure hydrocephalus is probably caused by cerebral atrophy.

Hence, examination of the patients with CM has revealed strong disturbance of CVOR that was normalized either partially or completely after surgical treatment. It is reasonable to conduct ultrasonography of cerebral venous circulation pre-, intra-, and postoperatively.

Conclusions

1. Patients with craniovertebral junction pathology (Chiari malformation) are likely to exhibit cerebrovenous orthostatic nonreactivity and moderate or significant hyperreactivity before surgical management.

2. After surgical treatment (decompression of the foramen magnum), patients with Chiari malformation exhibit significant normalization of craniovertebral volume ratios; cerebrovenous orthostatic reactivity is typically characterized by normoreactivity or, less frequently, by moderate hyperreactivity.

3. Venous flow velocity in the straight sinus in patients with craniovertebral junction pathology (Chiari malformation) may be increased before surgery and is normalized after surgical treatment.

Authors declare no conflict of interest.

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doi: 10.1016/S0140-6736(00)08407.
This paper focuses on the topical problem, studying the volume ratios between the craniovertebral junction structures and the features of the CSF dynamics and hemodynamics in this area in patients with Chiari I and II malformation during the preoperative and postoperative periods.

Chiari malformation is a common disorder that requires neurosurgical management in most cases. Nevertheless, the data on deep pathophysiological mechanisms of clinico-neurological disorders in this malformation have not been thoroughly studied yet. These factors are responsible for the scientific and practical value of the observations reported in this paper.

The study involved 35 patients with Chiari malformation. The venous blood flow in the straight sinus was registered in patients lying on the tilt table in the position varied between +90° and −30° (the original procedure was designed by the authors). It was found that either moderately or significantly increased cerebrovenous orthostatic reactivity (CVOR) (hyperreactivity) or no changes under orthostatic load (nonreactivity) was typical of patients with Chiari malformation in the preoperative period. Surgical management (decompression of the craniovertebral junction and dura mater reconstruction) normalizes CVOR, which is characterized by normoreactivity (63% of cases). Operative treatment is also found to normalize blood flow velocity in the straight sinus.

The material discussed and the conclusions drawn by the authors allow one not only to objectify the outcomes of neurosurgical treatment but also to reveal the key pathophysiological mechanism that is responsible for the type of pathology in patients with Chiari malformation. We believe that adding non-invasive ultrasound methods for assessing the condition of the craniovertebral junction to the algorithm of preoperative examination is reasonable and will improve early and delayed surgery outcomes. It will also allow one to specify the indications for surgery, which is particularly topical for Chiari malformation not accompanied by hydrocephalus or syringomyelia.

It should be mentioned that blood flow velocity in the straight sinus can be measured both intra- and perioperatively. There are Russian and foreign studies showing the relationship between the changes in these parameters revealed intraoperatively and the strategy of surgical intervention (decompression of the craniovertebral junction only or its combination with dura mater reconstruction). These studies can reasonably continue the work described in this paper.

A.O. Gushcha (Moscow, Russia)
Since the disability and mortality rates of hemorrhagic stroke are rather high, surgical treatment of the acute forms of cerebral circulation disorders still remains a very topical issue [2, 5]. The contribution of hemorrhagic stroke to the total structure of mortality is 1.28 per 1,000 population per year, which is significantly higher than the characteristics of other forms of cerebral pathology. The rate of this pathology ranges from 10 to 20 cases per 100,000 population and corresponds to approximately 45,000 hemorrhages per year [1, 2]. Most of them require adequate surgical management within the early period after disease onset [6].

A vast body of new experience in surgical treatment of hypertensive intracerebral hemorrhages (HICHs) has been accrued, offering an opportunity to reconsider the existing conceptions of treating this pathology [4, 6—8]. The existing methods, such as microsurgical removal, aspiration of hematoma, and local fibrinolysis have demonstrated fair outcomes of surgical treatment of hemorrhagic stroke in patients of different age groups [3]. As indicated by numerous studies [4, 6—8], the minimally invasive procedures for surgical treatment of patients with cerebral pathology are now commonly available for neurosurgeons.

The modern endoscopic systems meet all the key criteria that define minimally invasive surgeries, which undoubtedly is a significant breakthrough. Their development has made it possible to implement minimally invasive interventions in treatment of hypertensive intracerebral hemorrhages in actual practice [12].

L. Auer is the pioneer of endoscopic removal of intracerebral hematomas. In 1989, he demonstrated in a series of surgeries conducted in 100 patients that this method was preferred over conservative treatment of small and medium-sized hematomas (30—50 cm$^3$) provided that maximal radicality of their removal was achieved [10]. T. Nishihara [11] has demonstrated for 82 patients operated on that this method is promising when used early after stroke. C. Chen et al. [13] have also proved the effectiveness of endoscopic removal of hematomas of putaminal localization in 25 patients with GCS score of 3—12. The result of the surgical interventions performed by them consisted in reducing the mortality rate to 16%.

There are very few Russian studies focusing on endoscopic surgery of HICHs. One of those, the work by V.G. Dash’yan [7] reports management of 35 patients. According to findings obtained by A.B. Gekhtman [9] on the basis of the original prognostic scale of postoperative mortality among patients with HICH that he had developed, the endoscopic method proves to be most effective in patients with lateral hematomas if their volume is less than 50 cm$^3$. The mortality was 9% among the patients with the GCS level of consciousness score no less than 10. An analysis of the recent literature shows an increasing

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**Experience of Endoscopic Removal of Hypertensive Intracerebral Hemorrhage**

A.O. GUSHCHA, M.S. SEMENOV, L.T. LEPSVERIDZE

Scientific Center of Neurology, Moscow, Russia

This study focuses on our first experience (11 cases) of endoscopic removal of hypertensive intracerebral hemorrhage. The paper presents examples of endoscopic removal of hematomas located in the basal ganglia (9 cases) and hematomas located in the posterior fossa and causing occlusion at the fourth ventricle (2 cases). In 3 patients (27%) with intraventricular hemorrhage, the removal of acute hematomas from the ventricular system with simultaneous endoscopic third ventriculostomy (ETV) was performed. Intervention was carried out within the first 6 hours in patients with hemispheric hematomas (in 90% of cases) and within 3—5 hours, in patients with hematomas of the posterior cranial fossa. The article analyzes the functional outcomes in the early and late postoperative period. In our opinion, endoscopic removal of hypertensive intracerebral hemorrhage is a promising method that meets all the existing aspects of modern neurosurgery. The combination of rigid and flexible endoscopy provides new capabilities in surgery of patients with intraventricular hemorrhage.

**Keywords:** endoscopy, ‘chip-on-tip’ flexible endoscopy, hypertensive hemorrhage, hemorrhagic stroke.

**Abbreviations**

HICH — hypertensive intracerebral hemorrhage;
GCS — Glasgow Coma Scale;
IVH — intraventricular hemorrhage.
Table 1. Characteristics of the patients who had undergone surgical treatment

<table>
<thead>
<tr>
<th>No.</th>
<th>Localization of HICH</th>
<th>Hematoma volume excluding IVH, cm³</th>
<th>IVH, yes/no</th>
<th>Occlusive hydrocephalus, yes/no</th>
<th>For patients with IVH (Graeb scale), score</th>
<th>Time when the hemorrhage occurred, days ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Putaminal</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Thalamocapsular</td>
<td>36</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Putaminal-capsular</td>
<td>34</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Thalamo-putaminal-capsular</td>
<td>46</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Thalamocapsular</td>
<td>23</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Putaminal-capsular</td>
<td>26</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Thalamocapsular</td>
<td>32</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Putaminal</td>
<td>50</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Thalamo-putaminal-capsular</td>
<td>54</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>PCF</td>
<td>27</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>PCF</td>
<td>24</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
<td>3</td>
</tr>
</tbody>
</table>

Footnote. PCF — posterior cranial fossa.

Table 2. Key neurologic symptoms before and after surgical treatment

<table>
<thead>
<tr>
<th>No.</th>
<th>Neurological symptoms prior to surgery</th>
<th>Neurological symptoms after 7 days</th>
<th>Neurological symptoms after 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Obtundation, hemiparesis up to score 3, right horizontal gaze paresis</td>
<td>Hemiparesis (score 4), gaze paresis</td>
<td>Complete regression of all symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Obtundation, hemiplegia, gaze paresis, motor aphasia</td>
<td>Leg paresis — score 2, arm paresis — score 0</td>
<td>Arm paresis — score 2, leg paresis — score 3</td>
</tr>
<tr>
<td>3</td>
<td>Obtundation, dysarthria, hemiplegia</td>
<td>Leg paresis — score 2, arm paresis — score 0</td>
<td>Complete regression</td>
</tr>
<tr>
<td>4</td>
<td>Sopor, hemisyndrome, dysarthria, gaze limitation</td>
<td>Leg paresis — score 1, arm paresis — score 0, gaze limitation and paresis</td>
<td>Leg paresis — score 3, arm paresis — score 2</td>
</tr>
<tr>
<td>5</td>
<td>Obtundation, hemiparesis up to score 3, gaze paresis</td>
<td>Leg paresis — score 5, arm paresis — score 4</td>
<td>Complete regression of all symptoms</td>
</tr>
<tr>
<td>6</td>
<td>Obtundation, hemiplegia, gaze paresis, sensorimotor aphasia</td>
<td>Leg paresis — score 1, arm paresis — score 0</td>
<td>Leg paresis — score 3, arm paresis — score 3</td>
</tr>
<tr>
<td>7</td>
<td>Symptoms of occlusive disease, dysarthria</td>
<td>Dysarthria</td>
<td>No neurologic deficit</td>
</tr>
<tr>
<td>8</td>
<td>Obtundation, hemiparesis up to score 3, right horizontal gaze paresis</td>
<td>Hemiparesis — score 4, gaze paresis</td>
<td>Complete regression of all symptoms</td>
</tr>
<tr>
<td>9</td>
<td>Sopor, hemisyndrome, dysarthria, gaze limitation</td>
<td>Leg paresis — score 1, leg paresis — score 0, gaze limitation and paresis</td>
<td>Leg paresis — score 3, arm paresis — score 2</td>
</tr>
<tr>
<td>10</td>
<td>Symptoms of occlusive disease, dysarthria, mild hemiparesis</td>
<td>Complete regression</td>
<td>No neurologic deficit</td>
</tr>
<tr>
<td>11</td>
<td>Symptoms of occlusive disease, hemisyndrome</td>
<td>Complete regression</td>
<td>No neurologic deficit</td>
</tr>
</tbody>
</table>

Interest in endoscopic surgery of HICHs due to the generally improved outcomes of treating this disease.

In this study, we have demonstrated the results of employing the endoscopic method in treating patients with HICHs using rigid and flexible endoscopes.

The study was aimed at assessing the effectiveness of the endoscopic method in surgery of hypertensive intracerebral hemorrhages.

**Material and Methods**

The outcomes of surgical management of 11 patients with hypertensive hemorrhages aged 53–68 years and operated on during the period between March 2013 and December 2014 are reported. The patients were admitted to the Burdenko Neurosurgical Institute or transferred there from other neurological in-patient clinics; 8 (73%) patients were managed within day 1 since the onset of the disease; 3 (27%) patients were treated on day 3 or later. All the patients were either in compensated or subcompensated condition according to GCS: 2 (18%) patients, score 14; 6 (55%) patients, score 1; 1 (9%) patient, score 11; and 2 (18%) patients, score 10.

The following parameters were analyzed in all cases to determine the tactics of surgical treatment:

— level of consciousness and the presence of neurological deficit;
— time when the hemorrhage occurred;
— hematoma characteristics (volume, density, localization);
— Degree of IVH (according to the Graeb score) and severity of acute occlusive hydrocephalus, VCR II;
— presence of the dislocation syndrome and perifocal edema.

The main objective of endoscopic interventions was to improve the functional outcome and reduce the total mortality rate in the group of patients. We took into account the data of the prognostic scale of postoperative mortality among patients.
In terms of their localization, hematomas were subdivided according to the classification proposed by A.S. Saribekyan [6]. Table 1 shows the distribution of patients over hematoma characteristics.

The clinical symptoms and the dynamics of their changes during the postoperative period are listed in Table 2.

All patients underwent endoscopic surgeries using rigid and flexible optical devices. Karl Storz endoscopes, the GAAB systems, and a ‘chip-on-tip’ flexible endoscope were used. Diameters of working ports through which surgical interventions were carried out were 6 and 8 mm (Fig. 1).

In patients who did not need to have blood removed from the ventricular system, the port was installed with allowance for minimal traumatization of associative conductors (Fig. 2). In all the patients with IVH accompanied by hemo-tamponade of ventricles, the port was installed from the standard site for third ventriculostomy. Flexible optical device that has a number of benefits was used to remove blood clots from the ventricular system and to perform endoscopic third ventriculostomy.

Compression and dislocation syndromes were indications for surgical treatment in the acute phase: aggravation of the degree of occlusion in patients with IVH and low effectiveness of conservative treatment accompanied by persistent neurologic deficit in patients in the delayed phase.

Intracranial pressure (ICP) monitoring was performed in all patients with IVH using the Liquo Gard system. Monitoring was stopped and the ventricular drainage was removed only within 24 h after ICP had normalized and the patient had undergone a test for closure of CSF drainage.

Results

On postoperative day 14, after the patients had either been discharged from the neurosurgical department or transferred to further rehabilitation, all patients showed regression of neurologic symptoms to some extent (Table 2).

Complete regression of neurologic symptoms was achieved in 4 (36%) patients; the remaining 7 (64%) patients had a
moderate disability by the time they were transferred, which allowed 5 (45%) of them to be able to independently support themselves within the room after a course of rehabilitation therapy.

In 9 (82%), hematomas were completely removed. Two (18%) patients underwent partial removal (in the group of medial hematomas with blood breakthrough into the ventricular system).

No recurrent hemorrhages were observed.

In 2 (18%) patients, after ETV and hematoma removal using a flexible endoscope, ICP monitoring showed that it normalized within 24 h, which enabled removing the ventricular drain 48 h after the surgery. In the patient who had undergone ETV and had had blood removed from the ventricular system but the hematoma had not been removed, the ICP normalized only on day 7 of follow-up.

Figures 3 and 4 show two examples of hematoma removal.

Discussion

According to [7, 13], endoscopic removal of HICHs is mostly used in patients with putaminal and lobar hematomas. Endoscopy significantly reduces mortality in this group of patients; however, if patients had not been properly selected, it may increase the number of patients with severe neurologic deficit because of inextricable problems associated with radical removal of hematomas. Foreign authors [11, 13] believe that the procedure substantially reduces the duration of surgeries and postoperative mortality rate; it is comparable with microsurgical treatment in terms of its effectiveness.

This method is known to be characterized by minimal invasiveness and traumatization; however, the fact that radical removal of hematomas in some cases and the challenges associated with intraoperative hemostasis significantly limit its application. Most publications are based on small series and the main focus is placed on the features of the technique and the available tools.

We realize that it is too early to draw conclusions. It is difficult to compare the series of endoscopic interventions performed by us to other ones because there is no single scale and interpretation of the previously published studies is challenging. In particular, based on the findings of the only article published in 2014 [7], patients with deep hematomas were subdivided into the putaminal and thalamic groups only, which limits the possibility of comparing the groups and conducting a more thorough analysis.

In the scientific community, there still is no shared vision regarding how the time and sufficient effectiveness of surgical treatment for patients with hemorrhagic stroke compared to conservative therapy. The fourth randomized study (STICH 2) is currently being carried out, which includes comparing the conservative and surgical treatments in patients with subcortical hemorrhages. However, we believe that comparing patients based on treatment method only, without taking into account its effectiveness in each particular group, may result in uncertain inference.

The outcomes for our series of patients are promising; however, we realize that the procedure needs to be tested for a greater number of patients in order to obtain statistically significant data.

Authors declare no conflict of interest.
REFERENCES


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Commentary

The study focuses on an important issue, surgical treatment of hypertensive intracerebral hemorrhages.

It is known that the question regarding indications for surgical intervention and selection of the method for hematoma evacuation that would be optimal for a specific patient remains most complex in managing patients with hypertensive intracerebral hematomas.

The authors have analyzed the initial experience of endoscopic removal of deep hematomas with supratentorial localization in 9 patients and cerebellar hematomas in 2 patients.

The absence of complications and the positive neurological dynamics in all patients attest to the fact that the authors have mastered the surgical endoscopy procedure.

Unfortunately, no technical details of surgeries were mentioned in the article, namely: 1) how did the authors overcome the challenges associated with navigation in the hematoma cavity in medium being the non-transparent due to the presence of blood and in the pockets being inaccessible for visualization? and 2) how did the authors achieve reliable hemostasis?

It is noteworthy that in most patients (67%), hematomas were removed within 24 h after the hemorrhage; no recurrent hemorrhages were observed in these patients. Meanwhile, it is known for sure that the risk of postoperative recurrent hemorrhage and spontaneous hematoma expansion is the highest within 24 h after hemorrhagic stroke, primarily due because of the hemodynamic instability and a tendency towards arterial hypertension in this cohort of patients. In many clinics, this circumstance, provided that the patient’s condition is stable, is the reason for refusing surgery on day 1 of hypertensive intracerebral hemorrhage in order to correct high blood pressure.

In general, taking into account the fewness of publications focused on endoscopic removal of intracerebral hematomas, there is no doubt that this article is relevant today.

Further studies are required in order to select more patients to have a representative group, compare the endoscopic method of hematoma removal to other procedures, and draw more reliable conclusions.

Yu.V. Pilipenko (Moscow, Russia)
Classic spondylogenic cervical myelopathy (lower spastic paraparesis, flaccid paresis of the upper extremities, sensory conduction disorders) has rather low incidence. As a rule, patients seeking medical help have one or more of the following symptoms:

— movement disorders (decrease in strength, increased tone and spasticity in the legs, ataxia, etc.);
— sensory disorders (decrease/disruption of pain, joint and muscle sensitivity, etc.);
— reflex disorders (increase/reduction in tendon reflexes of arms and legs, abnormal plantar and carpal signs: Babinski, Rossolimo, Hoffmann).

Progressing degenerative changes in the spine and subsequent narrowing of the spinal canal are the most common causes of development of myelopathic presentation of the disease. Chronic compression of the spinal cord and roots causes ischemic changes in the nervous tissue.

Nowadays advances in the medicine allow nearly all patients with degenerative disorders of the cervical spine to undergo complex conservative treatment. Myelopathic presentation of the disease is typical for patients with long-lasting illness. The average time from the onset of clinical symptoms to seeking surgical help is 4 years. It should be noted that the number of patients seeking help form neurologists and neurosurgeons is growing every year.

Historically, the standard of care in spondylogenic myelopathy was cervical laminectomy. Over the time, however, this method has been replaced by more modern ones, and nowadays most surgeons prefer to perform decompression from the anterior approach (discectomy/corporectomy) [1].

Laminoplasty is one of the treatment options for spondylogenic myelopathy. The Z-shaped cervical laminoplasty was first described by M. Oyama et al. in 1973 [4] as a treatment for spondylogenic myelopathy due to spinal cord compression by the ossificated longitudinal ligament. Later the primary intervention has undergone numerous modifications and currently the most frequently used methods are those by K. Hirabayashi [2] and T. Kurokawa [12].

The aim of our research is to define indications for laminoplasty in patients with myelopathy and to analyze early and long-term outcomes of the interventions.

**Material and Methods**

The treatment efficiency was analyzed in patients with cervical stenosis complicated by myelopathy. All patients were operated on using laminoplasty. Out of 30 patients, Hirabayashi laminoplasty was performed in 26 patients and Kurokawa laminoplasty was performed in 4 patients. The average age of patients was 58.4 years; the ratio of women to men was 9:21. According to neuroimaging, 26 (76%) patients had compression at three levels, 3 (18%) patients had stenosis at four levels, and 1 (6%) patient had compression along 5 levels. The diagnosis was based on the results of dynamic clinical and neurological examination, X-ray study, CT, MRI, SSEP, and TMS. Indications for surgical treatment included compression at three levels or more, myelopathic syndrome due to compression of the spinal cord, motor and sensory conduction disorders, and axial symptoms.
disorders, dysfunction of the pelvic organs, changes observed in SSEP and TMS. A prerequisite for laminoplasty was preservation of slight lordosis or straightening thereof. Absolute contraindications for surgical treatment included acute inflammatory diseases and obvious signs of segmental instability.

**Instruments used**

In addition to a standard set of surgical instruments for operations on the spine, we used high speed burr with diamond tips and ultrasonic bone scalpel (MisonixBoneScalpel) (Fig. 1).

**Surgical technique: laminoplasty**

A total of 26 patients were operated using Hirabayashi method under general endotracheal anesthesia. The position on the operating table: on the abdomen, upper limbs are placed along the body; the head is fixed in the «MAYFIELD» skull clamp. An EOC was used in all cases to map the surgical field and for intraoperative monitoring. Midline incision (8—10 cm in size) was performed above the spinous processes, and an electric scalpel was used to skeletonize the pedicle and facet joints of the adjacent vertebrae. Bleeding from soft tissue was stopped with gauze soaked in hydrogen peroxide solution and by bipolar coagulation. Yard retractor was inserted into the wound. Prior to the main phase of the surgery, we performed C4—C5 foraminotomy (Fig. 2, 3) as prophylaxis for C5 root palsy (incidence of 8% without foraminotomy).

After partial resection of the spinous processes (1/2 of the height), high-speed burr or bone scalpel was used to drill through the vertebral arches; a course of 2–3 mm (with the preservation of the internal cortical layer of the arches) was cut out on the opposite side. After cutting through, microsurgical instruments were used to remove the yellow ligament within the visible area to mobilize “arch — spinous process” complex. This complex was then lifted up as a whole and fixed with microplates and screws (6 mm). It is necessary to achieve visualization of the dural sac in all cases (Fig. 2). All patients were monitored in the intensive care ward for 24 hours after the surgery and the cervical spine was immobilized with Schantz collar for a period of 4 to 6 weeks [4, 9].

A total of 4 patients underwent laminoplasty according to Kurokawa: bilateral cut through the arches that was followed by central cut through the spinous process and its abduction. It expanded a section of the spinal canal, which was fixed in the predetermined position by metal-osteosynthesis.

Postoperative results were evaluated by both the diagnostic methods listed above (clinical and neurological examination, X-ray, CT, MRI) and by using the JOA scale, Nurick scale and Recovery rate scale [13, 14].

**Results and Discussion**

Unfortunately, modern surgical methods are not 100% effective in treatment of cervical spondylogenic myelopathy. Along with the increase in the number of patients with cervical myelopathy, there is an increase in the number of surgeries performed all over the world to treat cervical stenosis of various localization, and the increasing number of surgeries result in the increase in the number of patients for whom the surgery failed to provide expected outcomes.

Despite advance in and continuous refinement of spine surgery techniques, the issue of selecting the optimal surgical approach to treat spondylogenic cervical stenosis remains relevant. All currently used surgical methods have both advantages and disadvantages.

Laminoplasty, which is the subject of this paper, is a relatively new method of treatment of cervical stenoses. Since the method was first described in 1973, it has not received proper attention in the Russian surgical practice.

The main criteria for postoperative evaluation were: dynamics of clinical symptoms, increase in the anteroposterior section of the spinal canal and preservation of supporting ability.

The average time from the onset of the disease to the surgery was 45 months.

Prior to the surgery, all patients (100%) had symptoms of myeloplastic syndrome with varying degrees of severity (Table 1).

The JOA cervical myelopathy scale was used for objective assessment of neurological symptoms [13, 14] with subsequent calculation of the recovery rate. The average severity of myelopathy based on JOA scale was 8.27 points in the preoperative period and 11.18 points in the postoperative period (Fig. 4). Recovery rate in our group of patients was quite high: 43.2% [14].
One of the clinical indicators of the treatment efficiency was assessment of gait disorders (Nurick scale) [14]. The majority of patients (88%) had average values of motor disorders of I-III degree, while the clinical presentation of the disease in 2 (12%) patients corresponded to VI degree. The median value of disorders severity amounted to 2 points prior to the surgery and 2.7 points after it (Fig. 4). Therefore laminoplasty had a good clinical effect.

In addition to the clinical picture, we have calculated the diameter of the anteroposterior section of the spinal canal in the pre- and postoperative periods. The anterior starting point was the dorsal surface of the compression factor (ossified longitudinal ligament, herniated disc, marginal osteophytes), and the posterior point was the base of the spinous process. Average diameters of the spinal canal in patients without [3] and with cervical stenosis in our groups (before and after the surgery) are shown in Table 2.

Sagittal cross-section of the spinal canal after the surgery was measured by localizing software ClearCanvas Workstation 2.0. The anteroposterior size of the spinal canal has been increased by an average of 0.77±0.23 cm (Fig. 5 and 6). In one third of the cases, we have expanded the spinal canal more than 2-fold (Fig. 7, 8).

In addition to neuroimaging techniques, TMS and the resulting SSEP are widely used for diagnosis of spondylogenic myelopathy. TMS allows evaluating the function of corticospinal tract (Fig. 9).

The SSEP was used to assess the state of afferent pathways. Changes in the amplitude-time parameters of N13 and N20 components reflect the degree of dysfunction of afferent spinal cord pathways. The N13 component is the dorsal horns response and represents dysfunction of the central gray matter. Reduced amplitude of the N13 component during recording SSEP of the median, ulnar and radial nerves is pathognomonic for myelopathy. However, SSEP method does not allow assessment of the functional state of the motor tracts. Another drawback of SSEP is its inability to accurately pinpoint the level of spinal cord lesions (Fig. 10).

In patients with no clinical symptoms of the disease the decision to perform the surgery was based on the data of the neurophysiological monitoring (TMS, SSEP). The

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Table 1. Severity of neurological symptoms in patients operated on for cervical stenosis

<table>
<thead>
<tr>
<th>Neurological symptom</th>
<th>n (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper paraparesis</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Tetrapareses</td>
<td>17 (51%)</td>
</tr>
<tr>
<td>Sensory disorders</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Pelvic disorders</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Increase/decrease in reflexes</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Change of gait</td>
<td>17 (51%)</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>20 (60%)</td>
</tr>
</tbody>
</table>

---

Fig. 4. Evaluation of the neurological status of the patients on JOA and Nurick scales in the pre- and postoperative period (see text for the explanations).
Fig. 5. Calculation of the cross section before (a=0.91 cm) and after the surgery (b=1.45 cm). The sagittal and axial section at the C4—C5 level.
a — rough compression of the spinal cord; b — the spinal cord is decompressed, the front and rear subarachnoid spaces can be visualized completely.

Table 2. Spinal canal diameter at different levels in patients without cervical stenosis [3] and in our group in patients in pre- and postoperative periods

<table>
<thead>
<tr>
<th>Indicator</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average values in patients without stenosis, mm</td>
<td>14.3±1.6</td>
<td>13.9±1.6</td>
<td>14.0±1.6</td>
<td>14.0±1.6</td>
<td>14.1±1.4</td>
</tr>
<tr>
<td>Averages values in our group before laminoplasty, mm</td>
<td>11.1±1.3</td>
<td>10.6±1.5</td>
<td>10.8±1.7</td>
<td>11.0±1.3</td>
<td>10.6±1.3</td>
</tr>
<tr>
<td>Averages values in our group after laminoplasty, mm</td>
<td>18.4±1.9</td>
<td>19.3±1.7</td>
<td>19.7±4.9</td>
<td>19.9±4.3</td>
<td>19.5±3.3</td>
</tr>
</tbody>
</table>

Fig. 6. Calculation of the cross section before (a=0.84 cm) and after the surgery (b=1.93 cm). The sagittal and axial section at the C3—C4 level.
a — rough compression of the spinal cord; b — the spinal cord is decompressed, the front and rear subarachnoid spaces can be visualized completely.

Fig. 7. MRI of the patient B.
a — prior to the surgery. Rough compression of the spinal cord at the C2—C4 levels with the formation of myelodysplastic focus. Absolutely no visualization of the anterior and posterior subarachnoid spaces; b — after surgery. Decompression allowed visualization of the part of the anterior and the complete posterior subarachnoid space.
Fig. 8. MRI and MSCT of the patient Sh.

a — rough spinal cord compression by osteophytes at C5—C6 level; b, c — MRI and MSCT after the laminoplasty; despite the presence of the osteophyte, lifting of the posterior of the complex had created a complete decompression of the spinal cord.

Fig. 9. Transcranial magnetic stimulation, bilateral abduction of m. abductor pollicis brevis, m. abductor digiti minimi on the right revealed signs of bilateral disruption of conductivity along corticocervical tract: moderate at the left abduction, expressed in the study of the right hand.

Complications

A total of 3 (10.2%) patients have developed C5 paresis, which regressed on its own by the time of discharge. Analysis of foreign literature demonstrated that this complication have an incidence of 8% [6, 8]. For example, Sasai K. and T. Saito [10] had no deficit in the C5 root in a group with simultaneous foraminotomy, but 4 cases of C5 palsy in the group without foraminotomy at this level.

Taking into account the preoperative MRI data, 1 (3.3%) patient underwent laminoplasty at C3—C4, C6. A short-term post-operative outcome was good, but control MRI revealed increase in compression at C5 and presence of changes in the amplitude-time parameters, reflecting the degree of spinal cord dysfunction, as well as changes in time for central motor conduction along corticospinal tract were indicative of high risk of development of neurological symptoms, and laminoplasty was suggested to this group of patients to prevent myelodysplastic syndrome. In the absence of the above, the surgery was not suggested.

To eliminate segmental instability, functional X-rays were performed in all patients prior to the surgery. In the postoperative period, the follow-up examination 3—6 months after the surgery did not reveal any signs of instability in our group of patients (Fig. 11).
Fig. 10. SSEP examination demonstrated that stimulation of the median nerves result in preserved peripheral level responses. The components of brainstem-spinal and cortical levels are reduced and are recorded unreliably, with a significant increase in latency and reduction in amplitude, and are better expressed with stimulation on the right (with the increase in the central conduction time and N9-N11 interval). There is marked disruption of afferentation at spinal-brainstem level: expressed with stimulation of the right, rough with stimulation on the left.

Fig. 11. An example of the functional postoperative radiographs after 16 months.
Signs of segmental instability are absent.

Fig. 12. The MRI of the patient P.

a — MRI before the operation: the arrow indicates compression; b — MRI of the same patient 3 months after the decompression: the arrow indicates the preservation of compression at the level of C5; c — MRI after re-intervention: compression is eliminated.
the appearance of clinical symptoms (Fig. 12). Therefore, the primary surgery was later supplemented by C5 laminoplasty.

The control MRI of 1 (3.3%) patient revealed a tense hematoma with spinal cord compression, and the patient underwent revision surgery with good clinical outcome. In one case, a patient developed severe ataxia in the early postoperative period. The MRI examination revealed no surgical complications. The patient was referred to rehabilitation and achieved good clinical outcome.

Visual analogue scale was used to assess pain in the postoperative period; the average value amounted to 2—3 points, i.e. good outcomes.

Conclusion

Our results demonstrate the need for accurate and comprehensive analysis of the neurologic status, neuroimaging findings and data of neurophysiological studies in patients with cervical myelopathy. Laminoplasty, as an adequate method of treatment, is an alternative to anterior decompression. It is not inferior to it, and in some cases (expanded stenosis) have undeniable advantages. Correctly chosen treatment tactics can significantly improve the clinical status of patients in this group. Laminoplasty is fairly easy to perform and does not require any special technical skills from a neurosurgeon. Small financial costs associated with the surgery allow its implementation in local and regional neurosurgical hospitals. The method is the “golden mean” between major anterior decompressions (multilevel corporectomy with fixation) and standard laminectomy.

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Commentary

This article describes the initial experience of the authors in the use of expansive laminoplasty for treating cervical spinal stenosis.

The authors provide detailed description of both the procedure and the issues and complications associated with this type of surgeries. This is useful for Russian neurosurgery, where the use of foreign sources for daily improvement of their education is not a characteristic mode of behavior for practicing neurosurgeons.

Evaluation of advantages and disadvantages of the method presented by the authors in comparison with the anterior approach and elucidation of the indications for the intervention are not the main objective of this paper. The author of works ensures that with further accumulation of scientific advances in neurosurgical practice and follow-up data the team of Professor A.O. Guscha will present new papers on effectiveness and differential use of all methods for treatment of cervical myelopathy caused by spinal canal stenosis.

Yu.V. Kushel (Moscow, Russia)
Endoscopic Endonasal Surgical Treatment of Large Pituitary Adenoma Spreading into the Posterior Fossa

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The objective of the study was to develop the tactics of surgical treatment of large and giant pituitary adenomas spreading into the posterior cranial fossa. Material and Methods. A patient with a large hormonally inactive pituitary adenoma extending to the right cavernous sinus and the posterior cranial fossa. Results. Endoscopic endonasal resection of a large endo-supra-latero(D)-retrosellar pituitary tumor was conducted. Control MRI shows that the tumor was radically removed. Oculomotor disturbances were observed in the early postoperative period; they significantly regressed within 6 months. The article provides a detailed analysis of the world literature on the issue under discussion. Illustrative pre-, intra-, and post-operative photographs, as well as histological preparations in the early postoperative period; thet significantly regressed within 6 months. The article provides a detailed analysis of the world literature on the issue under discussion. Illustrative pre-, intra-, and post-operative photographs, as well as histological preparations are shown. Conclusions. Modern minimally invasive techniques make it possible to remove large pituitary adenomas (and other tumors) of the posterior cranial fossa using the endoscopic endonasal approach. These operations must be carried out at highly specialized institutions by surgeons who have vast experience in endoscopic transnasal surgery of skull base tumors.

Keywords: endoscopic endonasal surgery of pituitary adenomas, endoscopic endonasal surgery of the tumors of the posterior cranial fossa.

Pituitary tumors are typically benign. They often reach giant sizes and spread into the cavernous sinus, suprasellarly, and into the posterior cranial fossa [1]. Pituitary adenomas spreading into the posterior cranial fossa are extremely rare. In 2011, J. Malik et al. [2] have published a case report on a giant prolactinoma that caused instability of the craniovertebral junction. Bing Zhao et al. [3] have provided their findings about the high efficiency of the extended endoscopic transphenoidal approach in surgery of giant pituitary adenomas. In the Western researchers consider pituitary adenomas with one of dimensions larger than 4 cm as giant [4]. According to the classification used at the Burdenko Neurosurgical Institute, giant pituitary adenomas are those that have at least one of dimensions no smaller than 60 mm [5]. Before endoscopic endonasal neurosurgery had started to be actively applied, spreading of pituitary adenoma into the posterior cranial fossa was an indication for using the transcranial approach [6]. Today, due to the advance in new minimally invasive surgical techniques, it is possible to use the endoscopic transnasal approach to partially resect the tumor residing in the posterior cranial fossa [4]. In 2009, an article presenting a rare clinical case involving the resection of a giant pituitary adenoma spreading into the posterior cranial fossa through the retrosigmoid approach was published in the journal ‘Problems of Neurosurgery named after N.N. Burdenko’ [7].

In this article, we report our experience in resecting a large pituitary adenoma spreading into the posterior cranial fossa using the endoscopic endonasal approach.

Case history

A 33-year-old man was admitted to the Burdenko Neurosurgical Institute on November 17, 2010 to undergo surgical treatment of a pituitary tumor. Since August 2010, the patient has been having visual loss in both eyes and diplopia. Two year prior to being admitted to hospital, the patient had noticed sexual malfunction. Hormone testing has shown that the tumor is hormonally inactive. The neurological examination has revealed the chiasmal syndrome failure of the first and second branches of cranial nerve V on the left side.

Ophthalmic examination showed VIS OD=OS=1.0 and bitemporal hemianopsys. No oculomotor disturbances were detected. Funduscopy showed that the optic discs were discolored with clear margin and plethoric tortuous veins.

The preoperative Karnofsky score was 80.

MRI scanning showed a large endo-supra-latero(D)-retrosellar pituitary tumor. The retrosellar extracapsular portion of the tumor coarsely compressed the brain stem structures near the pons, mostly on the right side. The tumor infiltrates the right cavernous sinus, overgrows the right carotid artery, and compresses the chiasm. Tumor size is 51×37×29 mm (Fig. 1).

Endoscopic endonasal resection of the giant endo-supra-latero(D)-retrosellar pituitary tumor was performed on November 24, 2010.

The typical endoscopic approach to the projection of the anterior wall of the main sinus through the right nasal passage was used. The sinus and the floor of the enlarged sella turcica were trepanned. A moderately bleeding tumor of gray color and moderate density was exposed after the dura mater of the sella turcica had been opened. The tumor was removed using curettes and a suction device. Two small secondary (acapsular) nodes were detected after the suprasellar portion of the tumor had been resected; they were removed using the suction device. The tumor spread into the cavity of the right cavernous sinus and was removed using the suction device. The right carotid artery was surrounded on three sides by the tumor. The tumor retrosellarly spread as a separate large node through the posterior wall of the cavernous sinus into the interpeduncular cistern, mostly on the right side, and compressed the brain stem structures at this level. The initial portions of the tumor in the interpeduncular cistern were dense, stringy, and difficult to remove. In the posterior sections, this portion of the tumor was less dense and was removed using a suction device. The
The retrosellar portion of the tumor was covered with arachnoid mater, which has been successfully dislocated and coagulated. The tumor was resected using 0°, 30° and 45° endoscopes (Fig. 2).

Control helical CT was performed immediately after surgery while the patient was still anesthetized. It showed total resection of the tumor; the cavity of the resected tumor (endos-supra-latero(D)-retrosellarly) contained air. Air was also detected above both frontal lobes. No hemorrhagic complications within the area that had been operated on were revealed (Fig. 3).

Upward, downward, and lateral gaze was assessed during pre- and postoperative physical examination (score 0—5). The absence of defects was considered normal (score 0). Insignificant limitation corresponded to score 1. Limitation of gaze by 1/3 corresponded to score 2; by 1/2, to score 4; absence of voluntary gaze corresponded to score 5. The presence and severity of ptosis was also assessed using score 0—5 [8].

The patient developed right oculomotor nerve palsy on postoperative day 1: upward, downward gaze, and inward eye movement was assessed as score 5; outward eye movement was completely preserved. The total score of oculomotor nerve palsy was 19 (Fig. 14).

It is most likely that the right oculomotor nerve was partially injured when the tumor was resected from the right cavernous sinus area.

Two weeks after the surgery, signs of partial regression of oculomotor nerve palsy were detected.

The follow-up MRI scans (postoperative day 13) showed that the tumor was resected radically, no contrast agent accumulation was detected (Fig. 5).

According to histological examination, it was a pituitary adenoma with nuclear polymorphism (Fig. 6).

Follow-up MRI scan 6 months after surgery showed no tumor recurrence and complete decompression of brain stem structures (Fig. 7).
Fig. 3. Helical computed tomography immediately after surgery: total resection of the tumor (see description in the text).

Fig. 4. The first day after the surgery. Third nerve palsy developed on the right side.

Neuro-ophthalmological examination 6 months after surgery showed further regression of right oculomotor nerve palsy; the total score of its lesion was 12 (Fig. 8).

Discussion

According to [9], no more than 5% of giant pituitary adenomas spread into the posterior cranial fossa. The treatment tactics for these adenomas is complex and ambiguous. Conservative treatment with dopamine agonists is indicated for prolactinomas spreading into the posterior cranial fossa. Surgical interventions through the retrosigmoid approach have been proposed in other cases [7].

M. Koutourousiou, P. Gardner (2013) and M. De Paivo Neto (2010) believe that surgical treatment of giant pituitary adenomas is a challenge for neurosurgeons. It is particularly difficult to resect tumor fragments with the parastem localization. Conservative management under certain indications and probably radiation therapy usually play a key role in achieving long-term remission [4, 10].

The extended transsphenoidal approach ensures panoramic visualization, which is required to remove tumors similar to the one described in our case report.

Today, despite the numerous positive aspects of the transsphenoidal approach, this surgical procedure is not completely devoid of postoperative complications. According to the literature data, the frequency of nasal liquorrhea in transsphenoidal surgery is 6—20% [11—13]; both conservative and surgical treatments are used. Paresis of the craniocerebral nerves is an appreciably common complication after tumor resection through the extended transsphenoidal approach [11]. In our case report, right oculomotor nerve palsy that emerged in the postoperative period regressed to a significant extent 6 months after the surgery.
Fig. 5. T1-weighted MRI scan on day 13 after the surgery.
Total resection of the tumor and decompression of brain stem structures. Hemostatic and plastic material (fragment of the fascia lata) is visualized near the sella turcica. A fragment of adipose tissue is detected in the basilar sinus.

Fig. 6. A histological specimen.
a—×200; b—×400. Pituitary adenoma: a monomorphic tumor with the predominantly solid architecture and few perivascular rosettes. Hematoxylin and eosin staining.

Fig. 7. MRI scan 6 months after the surgery.
Total resection of the tumor. Plastic material (fascia lata) is visualized in the basilar sinus.
Our clinical case was characterized by spreading of a large tumor into the posterior cranial fossa through the right cavernous sinus (most likely, along the trigeminal nerve) and successful resection of a large fragment of the tumor with parasellar localization through the endoscopic endonasal approach.

Conclusions

1. Modern minimally invasive procedures allow one to resect large pituitary adenomas (among other tumor types) from the posterior cranial fossa through the endoscopic endonasal approach.

2. These surgeries need to be performed at specialized medical centers by surgeons who have vast experience in endoscopic transnasal surgery of skull base tumors.

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Surgical treatment of patients with pituitary adenomas still poses a serious problem in modern neurosurgery. Although the development of sparing minimally invasive endoscopic transsphenoidal surgical approaches in 1993 made it possible to solve the problem associated with surgical management of pituitary adenomas to a significant extent, it is still difficult to ensure reliable control over resection of tumors from the parasellar and retrosellar areas. Further development of endoscopic techniques, wide implementation of endoscopic equipment, the experience of using extended approaches in endoscopic surgeries have allowed surgeons to help most patients, regardless of the size and growth direction of pituitary adenomas.

In general, the wide use of the endoscopic methods has made it possible to significantly broaden the indications for transnasal interventions, which has been proved in many studies. Nowadays, up to 95—97% of patients with pituitary adenomas, including giant ones, need to be operated on through the transnasal approach. This is also facilitated by the extended transsphenoidal and endoscopic approaches that have recently started to be used and allow one to resect not only pituitary adenomas but also other sellar and parasellar structures as well. Due to the permanent advance in endoscopic techniques, accumulated surgical experience, development of the modern methods for plastic reconstruction of skull base defects, the extended transsphenoidal endoscopic approaches are used more commonly instead of a series of open intracranial interventions and improve surgical outcomes. However, tumors spreading into the posterior cranial fossa still impose a challenge for neurosurgeons, since this type of pituitary adenoma is appreciably rare, involves numerous functionally important structures, and requires one to use the exclusively delicate surgical technique.

In this regard, the present article about the outcomes of endoscopic treatment of retrosellar pituitary adenoma is undoubtedly extremely relevant, is being waited for and highly demanded. Its authors are among the recognized leaders in endoscopic surgery of pituitary adenomas as they have the vast experience based on the broad data received at clinics of the Burdenko Neurosurgical Institute, one of the key centers for treating the neuroendocrine pathologies.

Based on the vast clinical material, the authors have approached solving a specific clinical problem being fully-armed. Having chosen the optimal yet challenging approach for resecting the tumor, they demonstrated a successful result. However, I would like to join the authors' warning that this solution to the problem should not be used in a wide range of in-patient clinics, since this intervention requires vast experience and a well-coordinated team of endoscopic surgeons. This type of treatment lies within the competence of specialized clinics. Although many Russian hospitals have had some experience in conducting endoscopic surgeries, it is still very limited in most of them and amounts to single surgeries or, less frequently, dozens of surgeries, whose outcomes are far from being optimistic. According to the published data, there are only 4 in-patient clinics worldwide where neurosurgeons have carried out over 1,000 endoscopic transsphenoidal interventions. To our country's credit, two of these clinics are located in Russia, in Moscow and St. Petersburg. The vast experience in conducting a great number of endoscopic transsphenoidal interventions allows neurosurgeons to achieve high-quality outcomes.

Further improvement of endoscopic technique, in combination with the vast experience in endoscopic transsphenoidal interventions demonstrated by the authors, gives new incentive to improving the outcomes of surgery of pituitary adenomas, which will eventually increase patients' quality of life.
Prx-Monitoring Based Decision-Making About Decompressive Craniectomy in a Patient with Severe Traumatic Brain Injury. A Case Report

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The presented case illustrates a new approach to making a decision about decompressive craniectomy in patients with severe traumatic brain injury and intracranial hypertension. The approach is based on continuous assessment of cerebral autoregulation using Prx-monitoring in addition to monitoring of intracranial pressure and cerebral perfusion pressure. Prx-monitoring enables timely detection of autoregulation failure and provides the opportunity to make a decision about decompressive craniectomy before starting such aggressive methods of intensive care as hypothermia or barbiturate coma.

Keywords: intracranial hypertension, extended neuromonitoring, Prx-monitoring, decompressive craniectomy.

Intracranial hypertension remains to be a leading cause of high mortality and disability among patients with severe traumatic brain injury (TBI) [1–4, 6]. Its incidence among comatose TBI patients ranges from 40 to 60% [6–8]. Neurosurgical techniques occupy a special place in the arsenal of methods of correction of intracranial hypertension. They include evacuation of intracranial hematomas, external ventricular drainage, and decompressive craniectomy [1–3, 6]. Along with elimination of secondary brain damage factors, timely diagnosis and prompt evacuation of pathological intracranial masses are important components of TBI patients’ treatment. Brain imaging techniques, such as CT and MRI, are key diagnostic tools for neurosurgical problems [3–5]. Indications for neurosurgical intervention include assessment of volumetric criteria and their dynamics: volume of pathological substrate, degree of the basal cisterns compression and displacement of the midline brain structures, etc. [1, 4, 5]. The main mechanism of decompression is the creation of additional space to compensate for the increased intracranial volume [6–8, 11]. The effectiveness of decompression is depended on the size of decompression window [9–11]. Intracranial pressure (ICP) monitoring is an additional factor in deciding whether to perform decompressive craniectomy. ICP above 20 mmHg that cannot be relieved by intensive therapy (sedation, anesthesia, hyperventilation, hyperosmolar solutions) requires more intense conservative therapy and/or decompressive craniectomy. ICP parameters, such as average value and duration of increase above 20 mmHg, were used in the two most recent randomized studies featuring decompressive craniectomy [12, 13]. These studies had different designs and inclusion criteria and used different limits for value and duration of intracranial hypertension to decide on decompression. These studies arbitrary divided the timing of decompression procedures into early secondary or neuroprotective and deferred secondary, in which the neurosurgical intervention was considered as the last stage of intracranial hypertension correction [14].

In our clinical case, we used pathophysiological approach to addressing the issue of decompression based on enhanced monitoring of ICP, cerebral perfusion pressure (CPP) and Prx autoregulation ratio [15]. The patient belonged to a group of TBI patients for whom the decompression was performed due to decompensation of cerebral vessels autoregulation and the development of intracranial hypertension [15]. The presence of decompensation and the lack of further options for conservative therapy were evaluated based on the dynamics of Prx ratio above 0.2. The autoregulation of cerebral vessels was assessed using Prx correlation ratio. Prx was calculated using the ICM Plus software (Cambridge, UK) and represents the correlation between the ICP and ABP. The Prx was calculated automatically as a moving average of 40 consecutive ICP and BP values, using 5-second window. Prx values of 1 to 0.2 were indicative of intact or partially intact autoregulation. Prx values of 0.2 to 1 were considered to be signs of complete autoregulation failure.

Clinical case

The first 24 h after the injury. The patient was a man (39 years) who sustained an injury in a fall from an ATV. He lost consciousness at the site of the accident and was transferred to the city hospital. At the time of admission he was in stupor (9 points on the Glasgow Coma Scale, GCS) with episodes of psychomotor agitation. Oval pupils along the midline, weak pupillary light reflex in both eyes. Left-sided hemiparesis. CT revealed bilateral lesions in the frontal lobes and in the left temporal lobe and convexital subarachnoid hemorrhage (SAH). Moderate swelling at the expense of the left hemisphere, visible cisterna ambiens. The ventricular system and subarachnoid space were narrowed. Tracheal intubation and artificial lung ventilation (ALV) due to increasing respiratory failure and the need for sedation. BP 130/80 mmHg, HR 108 bpm. The patient was ventilated and administered sedatives, decongestants, and antibiotics.

Day 2. The patient was transferred to the Burdenko Neurosurgical Institute. Diagnosis: a severe open TBI. Severe brain contusion with multiple foci of lesions (33 types) in the frontal lobes on both sides and in the left temporal lobe. Linear fracture of the occipital bone on the left with the transition to the base. Traumatic SAH. CT examination produced the same pattern (Fig. 1).
Neurological examination: 9 points on GCS, persistent probing resulted in a hand grasp. Brisk pupillary light reflex, presence of corneal reflex, reflexive upward gaze in response to irritation. The patient was able to hold his lower jaw, brisk cough reflex. Persistent motor anxiety, stereotypical movements. BP in the range of 120—130/60—70 mmHg, HR 80—90 bpm. Mechanical ventilation in SIMV mode, RR 10, Vt 0.8 L, PS 14 cm H2O, PEEP 6 cmH2O, FiO2 40%. Taking into account the data of CT examination, acute phase of severe TBI and the need for sedation, it was decided to monitor ICP. Parenchymal sensor revealed ICP of 25—29 mmHg, and ICP amplitude above 7 mmHg. The patient was on mechanical ventilation in BTPS mode, intracranial hypertension was corrected and CPP was maintained above 60 mmHg. He was administered 100 µg/h of fentanyl and 150 mg/h of propofol. Vasoressor support to control CPP included 1 mg/kg of body weight of mannitol, which was administered if ICP rose above 20 mmHg.

Day 3. Examination 30 minutes after turning off the sedation and narcotic analgesics revealed markedly negative dynamics: rough oral-stem syndrome which manifested as Magendie sign, oval pupils, limited reflexive upward gaze, hypersalivation. Swallowing movements and cough reflex sharply depressed. Low muscle tone in the limbs. Neurological examination was discontinued due to episodes of ICP elevation to 30—35 mmHg, which was alleviated by hyperventilation, reinitiation of sedation and analgesia in the previous doses, and additional infusion of mannitol (15%, 400 ml). It was decided to forgo the awakening test in the future. Osmolarity and sodium levels in the plasma were normal. Ventilation, SIMV, RR 14, Vt 0.78 L, PS 14 cm H2O, PEEP 6 cm H2O, FiO2 40%. Et CO2 30 mmHg. Low-grade fever up to 37.7—38 °C throughout the day. Controlled normothermia (36.5—37 °C) was performed using TroppyCool external cooling system. Hemodynamics was maintained by vasoressors (phenylephrine 8—10 mg/h). BP 135—165/70—90 mmHg. According to the neuromonitoring (Fig. 2), ICP 18—35 mmHg, CPP 60—95 mmHg, Prx 0.5—0.1. CT was not repeated due to unstable hemodynamics and intracranial hypertension, which was provoked by any manipulations and changes in the patient’s position. Tracheostomy was postponed until stabilization of the patient. Conservative therapy with neuromonitoring.

Fig. 1. CT data on days 2–3 after the injury.

![CT data on days 2–3 after the injury.](image)
Day 4. Repeated episodes of intracranial hypertension involving a plateau of ICP waveforms up to 40 mmHg, a short-term CPP drop below 50 mmHg during the plateau. Dynamic monitoring revealed a steady trend towards an increase in Prx above 0.2, indicating a failure of cerebral autoregulation (Fig. 3).

Sedation was deepened: propofol 250—300 mg/h, fentanyl in the previous dose, deep hyperventilation to EtCO2 of 28 mmHg under the control of jugular oximetry (Svo2 no lower than 50%). Sodium 145—149 mmol/l. Osmolarity 310 mOsm/l. The 15% mannitol solution was used four times during the day (1600 ml in total). A decision to perform decompressive trepanation was taken after a joint discussion with neurosurgeons. Surgery: decompression craniectomy of the frontoparietal-temporal area on both sides. Removal of subdural hy-
groma on the left (30 ml). Dura mater was repaired with perios-
teal flap on the left.

**Days 5—6.** Stabilization of ICP at 5—12 mmHg, CPP at 60—65 mmHg, and Prx >0.2 was observed in the postoperative period (Fig. 4).

Propofol dose was reduced to 80 mg/h, fentanyl was dis-
continued, phenylephrine dose was reduced to 5 mg/h. Con-
trolled normothermia was discontinued, low-grade fever of 37.8
°C. Examination without sedation: 6 points on GCS, right arm
adduction with flexion, without a distinct localization, slight
right leg adduction. Passive opening of the eyelids revealed eye-
balls fixed in the central position, oval pupils, weak pupillary
light reflex, weak corneal reflex on both sides, rare blinking
movements. The lower jaw droops, excessive salivation from the
mouth, tongue protrudes beyond the line of incisors, edema-
tous. Presence of lower jaw reflex. BP 120—145/85—80 mmHg,
HR 65—90 bpm, sinus rhythm. Ventilation, SIMV RR 14, Vt
0.75 L, PS 12 cmH2O, PEEP 7 cmH2O, FiO2 40%. Symmetri-
cal bilateral lung breathing, rigid, slight bilateral weakening in
posterior basal section. Increase in inflammatory markers in
the blood: leukocytosis with left deviation, CRP 178 mg/l.
X-ray: bilateral pneumonia. Antibiotic therapy, taking into ac-
count the sensitivity of the flora. Transcutaneous dilated tra-
cheostomy.

**Days 7—11.** Stabilization of hemodynamics, discontinua-
tion of vasopression and sedation. Low-grade fever persisted.
BP 120—130/60—70 mmHg, HR 80—90 bpm. ICP 5—7 mmHg,
CPP 60—65 mmHg. Prx values 0 to –0.1, indicating recovery of
autoregulation. Neurormonitoring was stopped on Day 11.

**Day 12—20.** Regression of infectious and inflammatory
manifestations, normalization of body temperature, resolution
of bilateral pneumonia. Positive dynamics in neurological signs:
10 points on GCS, slight right-sided hemiparesis. The patient
was able to follow certain instructions: shake hands on demand,
actively gesticulate. Stable hemodynamics, respiratory rehabili-
tation, transferred to the CPAP 5 cm H2O, FiO2 = 25%,
PS 10 cm H2O.

**Day 30.** The patient regained consciousness and was dis-
connected from the ventilator. Stable hemodynamics. The pa-
tient successfully underwent the repairmen of dura mater in the
left fronto-parietal-temporal region 22 months later due to ap-
appearance of wound liquor. Later, ventriculo-peritoneal shunt
was installed on the right due to development of hydrocephalus.
The patient was discharged from the hospital after 5 months.
Neurological status: slight right-sided hemiparesis, sensory-
motor aphasia. Swallowing movement was restored and the
cannula was removed. The patient subsequently underwent re-
habilitation and recovery courses up to 2 times a year. After 12
months, the outcome was assessed as moderate disability based
on the Glasgow Outcome Scale.

**Discussion**

The presented clinical example demonstrates that in addi-
tion to the traditional of ICP and CPP monitoring, the moni-
toring of cerebral vessels autoregulation enable timely decision
to perform decompressive craniectomy. In the presented clini-
cal case, the persistent failure of autoregulation on Day 4 dem-
onstrated futility of further pharmacological control of mean
arterial blood pressure and therefore inability to ensure CPP
above 60 mmHg. Taking this into account, any attempt to im-
prove the ABP would lead to passive increase in ICP and fur-
ther reduction in CPP. Since there was still an option of using
hyperosmolar solutions, and, moreover, ICP was successfully
reduced by deepening sedation and safe deepening of hyperven-
tilation controlled by jugular oximetry, we can only assume that
in the absence of autoregulation monitoring, the intensive care
would have proceeded along the lines of further increase in ag-
gressiveness. However, in the given clinical situation, osmotic
diuretics could not be considered as a mean of prolonged intra-

![Fig. 4. Extended neuromonitoring data after the decompression.](image-url)
craniocerebral hypertension correction, since there was a tendency towards hyponatremia, and mannitol had already been administered in close to maximum doses. Other options to intensify intracranial hypertension treatment were hypothermia and barbituric coma. Barbiturates can effectively remove intracranial hypertension; however, the number of adverse events, caused by their use, outweighs their positive effect on ICP and CPP. Barbiturates are regarded as the last stage of aggressive intracranial hypertension therapy, and their use does not improve outcomes in TBI [16, 17]. It can be assumed that the use of barbiturates in the patient would have required higher doses of vasoressors and aggressive fluid therapy, which in itself could have led to various complications: pulmonary edema, renal failure, heart failure, cardio-vascular events, etc [18, 19]. Today, barbiturates are regarded as the last stage of aggressive intracranial hypertension therapy, and their use does not improve outcomes in TBI [1, 4, 6, 7, 16, 17].

Hypothermia has proven to be an effective method of correction of intracranial hypertension. However, international multi-center studies have not demonstrated improved outcomes with the use of hypothermia in comparison with traditional methods of intensive care [18]. It was noted, however, that the number of adverse events, associated with the use of hypothermia, is as high as that for barbiturates [19, 20]. Decompressive craniectomy is not a panacea, either, but in our clinical case it demonstrated its effectiveness in correction of intracranial hypertension and CPP stabilization. In addition, decompression made it possible to reduce the aggressiveness of intensive therapy by reducing the dosages of sedatives and catecholamines. We were able to discontinue narcotic analgesics, stop hyperventilation, discontinue administration of hypomolar solutions, and achieve normalization of sodium levels and recovery of autoregulation.

Therefore, we have demonstrated the possibility of using a new approach to making the decision to perform decompressive craniectomy in patients with traumatic brain edema and intracranial hypertension. The essence of the new approach is continuous assessment of cerebral vessels autoregulation using Prx values, in addition to such important neuromonitoring parameters as ICP and CPP. Prx-monitoring enables timely recognition of the cerebral vessels autoregulation failure and allows making the decision to perform decompressive craniectomy prior to escalating aggressive methods of intensive care (barbituric coma and hypothermia).

**Authors declare no conflict of interest.**

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The clinical case described by the group of authors presents new opportunities for neuromonitoring of patients with severe TBI. Modern software make it possible to continuously monitor the status of cerebral blood flow autoregulation using Prx values (pressure reactivity index), in addition to traditional monitoring of BP, ICP, and CPP [1].

The papers published in the last 5—7 years confirm that this neuromonitoring parameter is one of the leading and most actively used ones in decision-making about intensive care strategy in patients with acute cerebral injury. The interest in monitoring of cerebral blood flow autoregulation has significantly increased for several reasons. First of all, the method based on computer analysis of slow-wave fluctuations in BP and ICP is both widely available and relatively. This fact ensured wide spread of the method of autoregulation assessment in neurointensive therapy. Secondly, the importance of autoregulation monitoring has been highlighted in the International Recommendations for the management of TBI patients [2]. Thirdly, there was a need to tailor intense therapy to individual patients based on multiparameter neuromonitoring, taking into account the severity of the injury and the time that has passed since cerebral injury, age of the patient, concomitant somatic pathology, secondary brain injury factors etc. [3, 4].

Timely provision of surgical assistance, no doubt, remains the leading factor, defining the outcome in TBI patients. Decompressive craniectomy is a method of intracranial hypertension correction for this category of patients, especially in case of development of intracranial hypertension. Unfortunately, the timing of decompressive craniectomy is not defined. The use of variety of strategies, early “neuroprotective” or deferred decompression, did not demonstrate convincing benefits and did not produce the expected improvement in TBI outcomes.

The present work demonstrates a completely new approach that can be called pathophysiological and that is based on the assessment of autoregulation. According to the authors, the failure of cerebral blood flow autoregulation is an indication for decompressive craniectomy. It seems quite reasonable, since in the absence of autoregulation it becomes very challenging to maintain CPP against the backdrop of intracranial hypertension. By using this clinical case as an example, the authors were able to demonstrate clinical significance of using Prx in patients with severe traumatic brain injury. The results are clearly presented and thoughtfully discussed in the context of recent publications on this topic.

It seems reasonable to further study Prx autoregulation ratio and implement it into the complex of neuromonitoring measures in the most severe category of critically injured patients and to use it as a reference point for targeted therapy.

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REFERENCES


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Abstract: Traumatic brain injury is one of the main causes of mortality and severe disability in people of young and middle age. Comatose patients with traumatic brain injury are most difficult to manage. Adequate diagnosis of primary brain injuries, timely prevention and treatment of secondary injuries can reduce mortality and severe disabilities. These guidelines are based on the previous authors’ experience of participating in the development of international and Russian recommendations for diagnosing and treating mild traumatic brain injury, penetrating gunshot wounds to the head and brain, severe traumatic brain injury, and severe complications of brain injuries, including the vegetative state. Furthermore, we used the materials of the recently published international and national recommendations on diagnosis, intensive care, and surgical management of severe traumatic brain injury. The proposed recommendations focus on the organization of medical aid and diagnosis of severe traumatic brain injuries in adults and first of all are intended for neurosurgeons, neurologists, neuroradiologists, anesthetists, and resuscitators who are involved in treatment of this group of patients on a daily basis.

Keywords: severe traumatic brain injury, surgical management of traumatic brain injury, intensive care of traumatic brain injury.

Over 700,000 people in Russia acquire traumatic brain injury (TBI) annually; this condition is among the main causes of mortality and disability among people of young and middle age. Patients with consciousness suppression up to the comatose state (score 8 and less according to the Glasgow Coma Scale (GCS)) are the group most difficult to manage, which indicates that they have severe TBI. These recommendations were designed for this very group of patients as they require an interdisciplinary approach involving neurosurgeons, neurologists, anesthesiologists, resuscitators, intensive care experts, neurorehabilitationists, and radiologists. Adequate diagnosis of primary brain injuries, timely prevention and treatment of secondary pathophysiological responses and injury mechanisms can reduce mortality and severe disabilities of TBI [1—6].

These guidelines are based on the previous authors’ experience of participating in the development of international and Russian recommendations for diagnosing and treating mild traumatic brain injury [7—12], penetrating gunshot wounds to the head and brain [13], severe TBI [14], and severe complications of brain injuries, including the vegetative state [15, 16], as well as clinical guidelines [17—23]. Furthermore, we used the materials of the recently published international and national guidelines for the diagnosis, intensive care, and surgical management of severe TBI [24—32].

The proposed guidelines focus on the diagnosis and management of severe TBI in adults and first of all are intended for neurosurgeons, neurologists, neuroradiologists, anesthetists, and resuscitators who are involved in treating this group of patients on a daily basis. This document does not claim to systematically report all the aspects of diagnosis and treatment of the patients with severe TBI and bears a recommendative nature. The guidelines only represent the authors’ opinion on the most important and disputable topics. In clinical practice, there can be situations that stretch beyond these guidelines; hence, the final decision on the strategy for managing every single patient should be made by the physician who is in charge for the treatment.

Methodology

In order to compile the evidential base, we searched for publications in Russian, English, and German languages in the National Library of Medicine database (www.nlm.nih.gov). The search depth was 20 years. The quality and strength of the evidence was assessed by the consensus panel of experts in accordance with the ranking table (see Table).

No studies with the evidence level higher than level 2 were retrieved because of the ethical limitations that do not allow one to perform control group studies in situations that might require surgical management. Hence, the theses involving the options were formulated in most sections. For these reasons, readers need to clearly understand that the volume and level of the recommendations presented result from summarizing the available literature and are interpreted in compliance with the rules of evidence-based medicine [33—35].

1.1. Organization of neurotrauma care

1.1.1. Primary care for patients with severe TBI

Basic life support needs to be provided: breathing (recovery of airway patency, management of hypoventilation disorders (hypoxemia and hypercapnia)) and circulation support (management of hypovolemia, arterial hypotension, and anemia) (standard).

1.1.2. Hospitalization of the patients with TBI

Recommendations

The patients diagnosed with severe traumatic brain injury require hospitalization to the neurosurgery or neuro-resuscitation unit of the emergency care unit. If there is no neurosurgery or neuro-resuscitation unit in...
the region, the patients are hospitalized to the trauma or intensive care unit (recommendations).

The in-patient care department that the patients with TBI are admitted to needs to be equipped with a computed tomography (CT) scanner available 24 hours a day (standard). The neurosurgeons should be trained in rendering medical aid to patients with TBI (recommendations).

2.1. Examination of patients with severe TBI upon admission

Recommendations

Upon admission to the neurosurgery or neuro-resuscitation unit, patients undergo thorough clinico-neurological examination that includes assessing the level of wakefulness according to the Glasgow Coma Scale (based on speech production, response to pain, and eye opening), which correlates with the degrees of suppression of consciousness used in Russia: score 15 according to the GCS corresponds to clear consciousness; score 13—14, moderate obtundation; score 9—10, semicoma; score 6—8, moderate coma; score 4—5, deep coma; and score 3, terminal (atonic) coma. Local, oculomotor, pupillary, and bulbar disorders are also assessed. The severity of patient’s condition is assessed according to examination by a neurosurgeon, anesthetist-resuscitator (in needed, traumatologist and surgeon) and the data of instrumented and laboratory examination (electrocardiography, X-ray, blood tests). Clinico-neurological and instrumented examination are carried out over time.

2.1.1. Neuroimaging in patients with severe TBI

The mechanism of a traumatic injury, its area, and degree of damage to the brain and head need to be elucidated in patients with TBI. Various neuroimaging methods play a crucial role in revealing the damage, its classification, assessing the area affected, and sorting the patients for emergency surgical interventions or conservative treatment. The modern methods of computed and magnetic resonance imaging allow one to deeper understand the pathophysiological mechanisms of injury and identify the primary and secondary brain damage [36—43]. The international and national neuroradiology associations have recently developed and published recommendations and monographs focused on the use of the entire range of modern neuroimaging methods for patients with TBI, including X-ray CT imaging, magnetic resonance imaging, angiography, single-photon emission computed tomography, ultrasonic methods, etc. [22, 23, 29—32, 44, 45, 47]. In these recommendations, let us focus on the neuroimaging methods that are most typically used for patients with severe TBI.

2.1.1.2. X-ray diagnosis methods

X-ray imaging remains a useful technique in diagnosing injuries to bone structures, penetrating wounds, and intracranial X-ray-detectable foreign bodies. However, its role has become significantly lower as computed tomography started to be more common.

Today, X-ray computed tomography (CT) is the leading method in diagnosing TBI as it allows one to promptly detect and localize acute intracerebral hemorrhages, mass effect and edema, foci of cerebral contusion and crush injury, to determine the size and configuration of the ventricular system of the brain or skull fracture, and detect foreign bodies. Other advantages include its availability and compatibility with life support devices. Furthermore, CT shows low sensitivity in diagnosis of microhemorrhagic and non-hemorrhagic lesions typical of diffuse axonal injury, lesions localized in the structures adjacent to the skull base and cranial vault bones, acute ischemic and hypoxic disorders, and intracerebral hemorrhages in the subacute and chronic phases [22, 29, 43, 45, 46, 48—56].

Recommendations

Computed tomography is the method of choice for primary examination of patients in the acute phase of TBI of different severity (standard).

When performing CT, one needs to determine the presence, location, and volume of hemorrhages and hematomas; presence and the area of cerebral edema; presence, location, structure and the area of medullary contusion; position of the midline structures of the brain and the degree to which they shift; the condition of the CSF-containing system of the brain and cerebral cisterns; condition of the cerebral sulci and gyri; condition of the bone structures of the skull base and cranial vault (presence and type of fractures); condition and contents of the paranasal sinuses, and condition of soft tissues of the skull.

<table>
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<tr>
<th>Level of evidence</th>
<th>Type of recommendations</th>
<th>Description of publications</th>
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<tr>
<td>Level 1</td>
<td>Standards</td>
<td>Well-designed randomized controlled clinical trials, including reviews of such trials</td>
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<tr>
<td>Level 2</td>
<td>Recommendations</td>
<td>Well-designed clinical trials with the control group (non-randomized cohort studies, case-control studies, etc.)</td>
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<tr>
<td>Level 3</td>
<td>Options</td>
<td>Case series studies, comparative studies with the external control group (historical control), case reports, expert opinions</td>
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Repeated CT examination is recommended in patients with aggravated neurological status or increased intracranial pressure, especially during the first 72 h after injury in order to diagnose delayed intracranial hematomas, ischemic disorders, and brain swelling.

In patients with craniofacial injuries and suspected liquorhea, 3D reformatted CT images should be recorded in the axial, coronal, and sagittal views. X-ray or CT scanning should be performed for patients with suspected injury to the cervical spine or other polytrauma.

Pronounced hemodynamic instability (uncontrolled arterial hypotension, systolic blood pressure below 90 mm Hg under continuous infusion of vasopressors) is the relative contraindication for CT of the brain.

2.1.1.3. Magnetic resonance imaging of the brain

Magnetic resonance imaging (MRI) is not so widely used in patients with the acute phase of TBI yet due to a number of limitations and contraindications (metal implants, the need for using nonmagnetic devices for monitoring and mechanical ventilation, duration of the examination procedure, etc.). However, MRI has a higher sensitivity compared to that of CT in diagnosis of the injuries to the brain structures adjacent to the cranial vault and skull base bones, diffuse and local microhemorrhagic and non-hemorrhagic lesions of the corpus callosum, basal ganglia, thalami, and the brain stem, which are typical of diffuse axonal injury. MRI is also a more sensitive method for detecting acute hypoxic and ischemic brain lesions, subacute and chronic hemorrhages, as well as differentiating various types of brain swelling [35, 39, 40, 41, 54, 57—60].

Based on a series of studies carried out using different MRI sequences [38—40, 42, 60], a new classification of localization and severity of damage to the hemispheric and brain stem structures was proposed that included 8 levels:

1 — no signs of parenchymal lesions;
2 — foci of lesions of cortical and subcortical localization, white matter;
3 — corpus callosum lesion±2;
4 — uni- or bilateral damage to subcortical formations and/or thalamus±(2—3);
5 — unilateral damage to the brain stem at any level±(2—4);
6 — bilateral damage to the brain stem at the midbrain level ±(2—4);
7 — bilateral damage to the brain stem at the pontine level±(2—6);
8 — bilateral damage to the medulla oblongata±(2—7).

Every next level can include signs of the previous ones. The new classification of brain damage based on the MRI data has demonstrated that there is a highly reliable correlation with the severity of patients’ condition and outcomes of the injury; hence, it can be used to predict the outcomes of TBI [39—41, 45, 55, 56, 59—62].

Recommendations

MRI is indicated for patients with TBI when there is a mismatch between their clinical condition and the CT data. When choosing the MRI regimes and sequences, one needs to take into account the injury mechanisms, presence of focal or diffuse lesions, and localization of intracerebral hemorrhages and hematomas (options).

In addition to the routine MRI sequences, it is reasonable to use FLAIR, diffusion-weighted imaging and diffusion-tensor imaging to diagnose nonhemorrhagic brain lesions. The modern regimes of high spatial resolution gradient-echo sequences, such as SWI or SWAN, are used to diagnose microhemorrhage and hemorrhage in the late period after injury (options).

To diagnose diffuse axonal injury, it is reasonable to use dynamic diffusion-tensor imaging with qualitative assessment of fractional anisotropy parameters in the brain stem along the corticospinal tracts, in subcortical structures, and in the corpus callosum with 3D construction of the conduction pathway (options).

The conditions for performing MRI are as follows: no metal implants; no contraindications for transportation due to instability of arterial and intracranial blood pressure, seizures or psychomotor syndrome; capabilities for providing monitoring and continuing adequate intensive care (including mechanical ventilation) during transportation and examination (options).

2.1.1.4. Angiography

Angiographic examination is indicated in patients with suspected damage to intra- and extracranial vessels, which is typically observed upon skull base fractures, penetrating wounds, and concomitant cervical spine injury.

The use of CT or MRI angiography has significantly reduced the demand for routine angiography.

2.1.1.5. Ultrasonic testing

Transcranial Doppler ultrasonography is used to assess the linear blood flow velocity in major cerebral vessels and their resistance, which may show vasospasm or vasoparesis during the acute phase of TBI. Ultrasound scanning is also used intraoperatively to localize intracranial hematomas, cerebral ventricles, foreign bodies, etc.

2.1.1.6. Perfusion CT and MRI

Perfusion CT and MRI are used for mapping parameters of the volumetric cerebral blood flow, blood volume and cerebral blood flow velocity in different vascular basins and selectively in the cortical, subcortical and brain stem structures in order to refine the role of hemodynamic factors in pathogenesis and prognosis of the course of traumatic brain injury and optimize the treatment strategy [37, 63, 64]. These methods are employed in patients with severe TBI in combination with monitoring of intracranial and cerebral perfusion.
pressure under certain indications (see Monitoring of intracranial pressure and cerebral perfusion pressure).

2.1.1.7. MR spectroscopy, functional MRI, single-photon emission computed tomography, and positron emission tomography is currently not used on a routine basis in patients with severe TBI.

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Commentary

The steadily high incidence of severe TBI, significant mortality and disability levels, and the large number of currently performed studies make it necessary to create and constantly edit the recommendations for rendering medical aid to patients with severe TBI. These recommendations are devoted to all aspects of severe TBI: organizing medical care and diagnosis, intensive care and neuromonitoring, and surgical management. Being the leading experts in this field, the authors have analyzed the most modern literature and findings of the studies carried out both in Russia and abroad. Furthermore, they used the materials of the recently published national and international guidelines for diagnosis, intensive care, and surgical management of severe TBI.

The guidelines are written laconically using a good language style. A number of recommendations and standards have been refined compared to the previous editions. Unfortunately, for some points the data in the available literature are insufficient for formulating standards or recommendations, so the use of certain actions or procedures is optional in this case. Apparently, the status of some options will be changed to recommendations as new data are obtained in new studies.

The guidelines for severe TBI will be extremely useful for neurosurgeons, anesthetists, resuscitators, neurologists, and radiologists who deal with practical rendering this kind of medical aid to this group of patients that is difficult to manage, as well as for all the stages of training neurosurgeons and the related physician specialties.

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Evaluation of the Biological Behavior of ACTH-Secreting Pituitary Tumors Using Various Methods

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This literature review is aimed at studying markers obtained by various research methods to assess the biological behavior of ACTH-secreting pituitary tumors. This paper presents the clinical, laboratory, instrumental, histological, and immunohistochemical aspects of ACTH-secreting pituitary tumors. Histological method allows assessment of tumor structure and differential diagnosis from other pathological processes in the sella turcica. Immunohistochemical method enables determining the expression of multiple markers (fibroblast growth factors, matrix metalloproteinases, apoptotic factors, pituitary tumor transforming gene, and vascular markers), which reflect various processes of oncogenesis of studied tumors and, according to the authors, are promising with regard to prediction of biological behavior of corticotropinomas. Epigenetic investigations including the study of microRNA expression, proteomics, and transcriptomics are the novel methods in this area, which are expected to provide additional details regarding the prognosis of corticotropinomas. Therefore, the cumulative assessment using laboratory and instrumental methods and the study of immunoeexpression of microRNA-markers of malignant potential in corticotropinoma tissue will allow predicting the further biological behavior of ACTH-secreting pituitary tumors.

Keywords: ACTH-secreting pituitary tumor, evaluation and markers of malignant potential.

Pituitary adenomas are neuroendocrine tumors that originate from adenohypophysis cells. Previously, it was believed that pituitary tumors account for about 10% of intracranial tumors. However, significant improvement of radiological and hormonal diagnostic techniques increases the number of diagnosed cases up to 25%, and hormonally active corticotropinomas account for 10—15% of them [1, 2].

The course and clinical presentation of pituitary tumors are diverse (with excessive secretion of various hypophysiotropic hormones or without hormone overproduction). In both cases, extrasellar tumor growth can be accompanied by damage to surrounding structures of the central nervous system (CNS). The vast majority of pituitary adenomas (about 98—99%) are benign tumors. However, determining the prognosis of the further course of pituitary adenomas and effectiveness of various treatments is still an open issue. Thus, over the past few decades, there were many studies aimed at discovering markers that may be associated with pituitary adenomas and increased malignant potential, i.e. invasive growth into the surrounding CNS structures, the development of relapses after various treatments, and the appearance of metastases (in case of pituitary carcinomas). As a result, numerous molecular and immunohistochemical markers were discovered, which are indicative of the aggressive potential of pituitary adenomas.

The analysis of the biological behavior of corticotropinomas would be incomplete if we evaluated only disembodied data from different methods. It is important to evaluate the whole clinical presentation, the data of laboratory and instrumental methods. Assessment of the histological structure and immunophenotype of tissue samples from resected tumors enables the differential diagnosis between pituitary adenomas and other pathological processes in the sella turcica, determining hormonal and proliferative activity, receptor status, etc. To this end, molecular genetic techniques can additionally be used.

The analysis of clinical presentation and blood tests for the level of hypophysiotropic hormones are required to understand the tumor hormone production profile, assess disease activity and the results of treatment (clinical and biochemical remission or tumor progression after surgical, pharmacological, or radiological treatment) [3].

Magnetic resonance imaging (MRI) plays the most important role in assessing pituitary tumor size, growth direction, and involvement of the surrounding CNS structures. T1 MRI with 3 mm slice thickness is an optimal method to diagnose pituitary adenomas. Contrast-enhanced MRI is used for clearer visualization of microadenoma due to different vascularization of tumor tissue and intact adenohypophysis (adenohypophysis tissue accumulates contrast agent more intensively, while tumor tissue demonstrates “accumulation defect”) [4]. It is particularly important to note that MRI provides assessment of the presence of invasive growth. J. Trouillas et al. [5] demonstrated that the presence or absence of invasive pituitary tumor growth, as shown by MRI, is the main predictor (using multivariate analysis and ROC-curve) of remission or relapse after neurosurgical resection of the aforementioned tumors. It is also known that MRI is more valuable method to detect invasive growth compared to histological method. Histological examination can detect only 9% of invasive tumors [6].

Another problem with verification of corticotropinomas may be associated with the absence of tumor on MRI. In this situation, blood sampling from the cavernous sinus with desmopressin stimulation is recommended to confirm the ACTH-secreting pituitary tumor [3].

Histological examination of corticotropinomas with hematoxylin staining enables determining the histological structure of tumors and, if necessary, differential diagnosis with other pathological processes in the sella turcica: metastases, craniopharyngiomas, various cysts, inflammatory changes, hyperplasia of the adenohypophysis [7].

ACTH-secreting adenomas are typically characterized by intrasellar location in the middle sector of the pituitary gland. Macroscopically, corticotropinomas tissue is red, soft, and distinctive from a yellowish-brown dense pituitary gland.
Microscopically, it is sometimes difficult to distinguish between tumor tissue and the surrounding pituitary gland due to poor capsule or its absence [8]. According to electron microscopy data, corticotropinomas are represented by densely granular and sparsely granular tumors. Today, electron microscopy has been replaced by simpler and less time-consuming method of immunohistochemistry using antibodies to low molecular weight keratin CAM 5.2, as well as periodic acid Schiff (PAS) reaction. Densely granulated corticotropinomas consist of monomorphic round basophil cells with pronounced diffuse immunoeexpression of ACTH (about 60% of cells are monohormonal, while other can express various hypophysiotropic hormones and CAM 5.2). In these cells, mitoses are rare and Ki-67 index is low (under 1%).

Sparsely granular corticotropinomas consist of chromophobe cells characterized by diffuse growth and formation of sinusoidal structures around the capillaries. Cellular and nuclear polymorphism is often observed, there are signs of apoptosis, and mitoses are very rare. Immunohistochemical reaction with antibodies to ACTH is weak, tumor cell foci are stained, there is pronounced expression of CAM 5.2 and weak PAS reaction.

So-called Crooke’s cell adenomas are very rare. They consist of large chromophobes and eosinophilic cells with pronounced Crooke’s hyaline changes (accumulation of keratin results in glassy cytoplasm), which occur when pituitary cells are exposed to high levels of cortisol. Keratin deposition in cytoplasm results in shift of ACTH-positive granules towards the periphery of tumor cells or perinuclear space. Staining with antibodies to CAM 5.2 looks like a ring around cell nucleus. These large polymorphic cells must be differentiated from neurons of gangliocytomas or metastatic carcinomas at other sites. Immunoeexpression of Tpit (T-box transcription factor) gives evidence of differentiation of corticotroph cells [9].

In patients with Cushing’s disease (CD), the size of the tumor and its expansion in the sella turcica is not always associated with the severity of symptoms caused by excessive production of ACTH. Classical course of CD is usually associated with the presence of pituitary microadenomas (70—90%), whose histological examination reveals a densely granular corticotropinoma [9, 10]. Other macrocorticotropinomas have scarcely granular histological structure or represent adenomas with Crooke’s changes [11]. Macroadenomas are often characterized by cyclic clinical course, incomplete picture of hypercorticism, or lack of hormonal activity with a tendency to tumor progression after various treatments. [12]

A careful examination of the tissue surrounding the pituitary tumor may provide additional information. In cases where there is no pituitary tumor in surgical material, histological study can reveal the presence of Crooke’s changes in pituitary tissue outside the tumor. This gives an evidence of hypercortisolemia, which affects the adenohypophysis cells in this way [9, 13, 14].

Resection of corticotropinomas gives rise to the question of further disease prognosis.

Classification of the WHO in 2004 [8] identifies typical and atypical pituitary adenomas and pituitary carcinomas. Diagnostic criteria of typical adenomas include negative immunoeexpression of p53, Ki-67 index below 3%, and low mitotic activity. Atypical adenomas are characterized by excessive immunoeexpression of p53, Ki-67 index above 3%, and high mitotic activity. The principal difference between carcinomas and pituitary adenomas lies in the presence of craniospinal and/or distant metastases.

The study of tissue samples of 121 pituitary adenomas by G. Zada et al. [15] revealed 15% of atypical adenomas: hormonally active (somatotropinomas, n=32, 5 of them were typical, corticotropinomas, n=12, 2 of them were atypical, prolactinomas, n=18, 2 of them were atypical) and inactive tumors (n=58, 9 of them were atypical). However, there was no dynamic follow-up of patients after tumor resection.

The study of W. Saeger [7] revealed significantly lower amount of atypical adenomas. A total of 451 pituitary adenomas have been studied, 12 (2.7%) of them were atypical. Atypical adenomas were represented by 3 somatotropinomas, 1 prolactinoma, 3 corticotropinomas, 1 gonadotropinoma, 3 null cell adenomas, and 1 plurihormonal adenoma. This discrepancy can be explained by the fact that different criteria were used to assess the results.

Some experts suggest adjustments to the classification of pituitary adenomas, which would takes into account the clinical presentation and the data of laboratory and instrumental studies, the results of surgical treatment, and further course of the disease.

G. Raverot et al. [6] suggest more detailed clinical and pathological classification of pituitary tumors, which is based on the following characteristics.

1. Tumor size on MRI: microadenomas (less than 10 mm), macroadenomas (more than 10 mm), and giant tumors (more than 40 mm)


3. The stage of tumor development according to the following criteria:

   - invasive tumor growth into the cavernous or sphenoidal sinuses according to histological examination and MRI;
   - proliferative activity based on the presence of two of the three attributes: mitoses (2 in 10 fields of view); Ki-67 index not less than 3%; positive P53 (more than 10 stained nuclei in 10 fields of view);

   Based on these characteristics, three are three stages of tumor development:

   - 1a — non-invasive;
   - 1b — non-invasive and proliferative;
   - 2a — invasive;
   - 2b — invasive and proliferative
   - 3 — metastatic, with the development of cerebrospinal or distant metastases (pituitary carcinoma).

   The proliferative activity of pituitary adenomas can be assessed based on the most common markers (number of mitoses, Ki-67, and p53). Given the contradictory significance of these markers, especially Ki-67, underspecified methodological standards and P53 cut-off values, the authors of this classification suggest the use of at least two of the three criteria of proliferative activity: more than two mitoses per 10 fields of view and Ki-67 index not less than 3%, similarly to endocrine pancreatic tumors [16].

   The authors believe that this classification has weighty prognostic value regarding the postoperative period for all types of pituitary adenomas. If a patient has invasive and proliferating tumor (2b stage), the probability of tumor progression increased 12-fold compared to non-invasive and non-proliferative tumor (1a stage) during 8 years [17].

   Diagnosis of pituitary carcinomas posed some problems both previously and currently. It is believed that pituitary
carcinoma is a tumor derived from the adenohypophysis cells with proliferation of metastases into the central nervous system and distant organs (WHO classification, 2004). According to various reports, malignant pituitary tumors occur in 0.2—1% of cases with confirmed cranial and/or spinal metastases. In total, the literature [6, 18] describes 132 cases of pituitary carcinomas during 1961—2009. Most of them are hormonally active carcinomas: 36% of prolactinomas and 30% of corticotropinomas. Hormonally inactive carcinomas account for about 23%.

Macroscopic view of most pituitary carcinomas do not differ from that of invasive macroadenomas. The main features of carcinomas include the continued growth in the form of one or more subarachnoid nodules with invasion into the underlying brain tissue or dura mater.

The majority of malignant pituitary tumors demonstrate invasive growth into sella turica structures (dura mater, bones, cavernous sinuses, cranial nerves) and hypothalamus. The tumor spreads to the central nervous system through the cerebrospinal fluid. Systemic metastases spread through the hematogenous way via cavernous sinuses and jugular vein, which is accompanied by involvement of the liver, lungs, bones, adrenal glands, heart, and even ovaries. In the case of invasive growth into the skull base and soft tissues, the tumor is disseminated through the cervical lymph nodes.

No histological, immunohistochemical, and ultrastructural features, providing reliable diagnosis of malignant pituitary tumor, especially in cases where the tumor does not expand beyond the sella turica, have been discovered so far [19].

Microscopic structure of pituitary carcinomas is more or less similar to that of adenomas; the only distinctive feature is the presence of metastases. Mitotic activity may also vary and it is found in 3.9% of noninvasive adenomas, 21.4% of invasive adenomas, and 66.7% of carcinomas.

Both carcinomas and adenomas are immunopositive to various pituitary hormones (they typically express ACTH and PRL with development of corresponding clinical presentation), neuroendocrine markers (synaptophysin and chromogranin A).

When comparing the expression of tumor suppressor gene (TP53), adenomas were found to lack the expression of this marker, while 15% of invasive adenomas and 100% of carcinomas and their metastases demonstrated pronounced immunoeexpression. In many carcinomas, the presence of p53, p27, topoisomerase 2a (which regulates DNA replication), VEGF, and HER-2/neu was observed. Cell-cycle inhibitors are rarely observed in carcinomas compared to normal adenohypophysis. Ki-67 index is the highest in carcinomas (12%) compared to invasive (4.5%) and non-invasive (1%) adenomas [8].

The average survival of patients is 2 years and it is reduced to 1 year and below when metastases are detected. Continued growth of the tumor on MRI, growth of hypopituitarism symptoms or significant increase in hormone levels, disappearance of sensitivity to a dopamine agonists or somatostatin analogues are unfavorable prognostic factors.

In recent years, numerous investigations were conducted studying a large number of biological markers associated with unfavorable course of pituitary adenomas (invasive properties, tumor progression). However, no marker that could be used alone to determine the prognosis of the behavior of pituitary tumors has been discovered so far.

This literature review presents a number of biological markers (fibroblast growth factors, matrix metalloproteinases, apoptotic factors, pituitary tumor transforming gene, vascular markers), which can be detected by means of immunohistochemical studies and are considered as the most accurate prognostic markers with respect to biological behavior of pituitary adenomas.

Expression of the second and fourth types of fibroblast growth factors (FGF2, FGF4), regulating the growth, differentiation, cell migration, and angiogenesis, were found in the pituitary gland [21]. The highest expression of these factors was observed in corticotropinomas compared to somatotropinomas and prolactinomas. This may be due to the involvement of FGFs in the pathogenesis of ACTH-secreting tumors. The loss of FGF2 in the tumor results in activation of MAGE-A3 (melanoma-associated A3 antigen) [49] and modified FGF4 isoform, which lead to invasive growth of tumor cells in vivo and the loss of N-cadherin expression at the cell membrane. Moreover, modified FGF4 isoform interacts with NCAM (neuronal cell adhesion molecules), which is also associated with invasive properties of pituitary adenomas.

Matrix metalloproteinases (MMPs) are the family of single-stranded zinc-containing proteolytic enzymes that regulate the state of the extracellular matrix in physiological and pathological conditions. Eight various classes of metalloproteinases have been described, which include 24 functional types. MMPs penetrate into the extracellular matrix structures, such as collagen fibers, laminin, fibronectin, vitronectin, and proteoglycans. MMPs are produced by invasive tumor cells, fibroblasts, macrophages, etc. [20]. MMPs, in particular type 9 ones, destroy type 4, 5 and 10 collagen fibers, elastin, fibronectin, and proteins associated with proteoglycans. MMP2 and MMP9 are expressed by vascular endothelial cells and stromal cells. MMP9 expression was found in breast and lung malignant tumors. In pituitary adenomas, MMP expression is significantly higher than in invasive tumors [21—23].

Taking into account the aforementioned properties of fibroblast growth factor and matrix metalloproteinases, the study of these markers is believed to be promising with a view to determining the unfavorable prognosis of corticotropinomas.

The process of apoptosis in pituitary tumors is poorly known. Pituitary adenomas are tumors with low proliferative activity (a small number of mitoses, low Ki-67 index) and low level of apoptosis. Apoptosis and mitotic activity are inherently opposed processes. In tumors located at other sites, the balance between anti-proliferative activity and proliferation of tumor cells is usually shifted towards the latter. However, these processes are like-directed in pituitary adenomas. Pituitary carcinomas demonstrate high level of proliferation and apoptosis [24].

Due to low activity of apoptosis in pituitary adenomas, it is difficult to detect tumor cells with apoptotic changes using routine histological examination. In the early stages of apoptosis, pycnosis of nuclei and subsequent condensation of chromatin with irregular contours is observed. Cell size is reduced and cytoplasm becomes compact. The cells gradually lose contact with the surrounding structures. Then, nucleus fragmentation into small particles occurs accompanied by formation of pycnotic apoptotic bodies.

The process of apoptosis can also be studied by electron microscopy, immunohistochemistry, cytometry, and TUNEL-method.

Immunohistochemistry study shows that about 30% of various pituitary adenomas express Bcl-2. Bcl-2 is an intracellular protein factor that inhibits apoptosis in many cell
immunohistochemical reaction with anti-PTTG antibodies in most pituitary tumor cells, while nuclear reaction is observed compared to normal pituitary tissue, which is characterized by of genetic instability [31].

PTTG is involved cellular and tissue processes such as system organs (including pituitary tumors) and other systems. The gene is observed in many tumors derived from the endocrine systems, including lymphohematopoietic and neuronal cells and regulates cell death by controlling the permeability of the mitochondrial membrane. Almost all hormonally active and significant proportion of hormonally inactive tumors are immunopositive with respect to the pro-apoptotic bax protein. Disturbance of Bcl-2 and bax expression is observed in the pituitary tumors and plays an important role in regulation of apoptotic mechanisms. Among various pituitary adenomas, apoptotic changes are most often detected in corticotropinomas by electron microscopy. According to various studies, there is no significant difference in the level of apoptosis in pituitary microadenomas and macroadenomas. Several studies [25—27] have shown that expression of proapoptotic molecules bax and bad is reduced in invasive pituitary adenomas compared to non-invasive ones.

Interesting results were obtained by C. Tanase [28] in the study of functional proteins involved in apoptosis process (apoptotic protease activating factor 1 (APAF-1) and cathepsin-B) by immunohistochemistry with specified antibodies, western blot, and chemiluminescence. Cathepsin-B is a lysosomal protease, which contributes to disintegration of the extracellular matrix due to activation of MMPs and is also involved in activation of apoptotic genes and suppression of antiapoptotic ones. The study included tissue samples of 30 pituitary adenomas (16 of them were hormonally active and 22 had invasive growth) to compare APAF-1 and cathepsin-B expression in the groups of invasive and non-invasive adenomas. Invasive adenomas demonstrated reduced expression of APAF-1, which was associated with high Ki-67 index and positive expression of p53. Expression of APAF-1 and cathepsin-B demonstrated inverse mutual correlation. Increased expression of cathepsin-B was observed in invasive adenomas and correlated with high Ki-67 index and positive expression of p53.

In recent papers, another marker reflecting apoptosis process was described. Survivin is a member of the apoptosis inhibitor family. In these studies, the results of comparing survivin expression in normal pituitary tissue, invasive and non-invasive hormonally active pituitary adenomas using immunohistochemistry and PCR methods are reported. Overexpression of survivin in pituitary adenomas compared to normal pituitary tissue, as well as in invasive adenomas compared to non-invasive ones, was shown [29, 30].

Therefore, the study of extended marker panel will lead to better understanding of apoptosis and proliferation in pituitary tumors and will allow using them as predictors of poor prognosis.

Pituitary tumor-transforming gene (PTTG) is another important marker. Expression of pituitary tumor-transforming gene is observed in many tumors derived from the endocrine system organs (including pituitary tumors) and other systems. PTTG is involved cellular and tissue processes such as proliferation, DNA repair, stimulation and inhibition of apoptosis, activation of angiogenesis, invasion, and induction of genetic instability [31].

Pituitary tumors demonstrated overexpression of PTTG as compared to normal pituitary tissue, which is characterized by low expression or lack thereof [32].

Immunohistochemical study shows cytoplasmic reaction in most pituitary tumor cells, while nuclear reaction is observed more rarely. Several studies have shown that nuclear immunohistochemical reaction with anti-PTTG antibodies (along with mitotic activity, Ki-67 index, and p53) in pituitary tumor cells is a valuable prognostic marker related to biological behavior. X. Zhang [33, 34] and A. Wierinckx [35] discovered overexpression of PTTG micro-RNA in invasive hormonally active pituitary tumors. There was no correlation between PTTG expression level and the presence of invasion in hormonally inactive pituitary adenomas. M. Filippella et al. [36] discovered nuclear immunexpression of PTTG in 89% various hormonally active pituitary adenomas, which was significantly higher in recurrent tumors and correlated with Ki-67 index. Breakdown point for PTTG expression in recurrent and non-recurrent adenomas was 3.3% (60% sensitivity and 76% specificity). There was no significant correlation between PTTG immunexpression and tumor size, radiological picture, age, gender, or treatment of patients.

Some studies [30, 34, 37] focused on the relationship between PTTG expression and pituitary adenoma type. In the study of 40 pituitary adenomas (12 somatotropinomas, 5 prolactinomas, 5 corticotropinomas, and 18 hormonally inactive adenomas), significant increase in the expression of PTTG microRNAs was found in somatotropinomas compared to prolactinomas and corticotropinomas. It is believed that different level of PTTG expression depends on different molecular mechanisms triggering initiation and/or progression of a tumor, caused by PTTG.

In vitro studies showed the relationship between the expression of PTTG and fibroblast growth factors. Overexpression of these markers was found specifically in invasive pituitary adenomas [38].

C. McCabe [39, 40] showed significant positive correlation between PTTG and VEGF microRNA in 111 different types of pituitary adenomas. T. Minematsu et al. [41, 48] revealed the relationship between vascular density (determined using CD34 immunexpression) and PTTG in somatotropinomas. Based on these data, the authors concluded that PTTG is involved in angiogenesis of pituitary tumors through activation of VEGF. Interesting results were reported by E. Hunter et al. [37]. The correlation between expression of VEGF and S100, which is a Sertoli cell marker (alleged source of VEGF secretion) was detected.

The study of A. Heaney et al. [42] on four pituitary adenomas revealed decreased expression of PTTG, which was associated with decreased proliferative activity (PCNA) and Bcl-2.

Thus, pituitary tumor-transforming gene is an integrative marker of the most important processes of carcinogenesis in pituitary tumors.

In tumors derived from various organs (mammary gland, ovaries, bladder, thyroid, and pituitary gland), chromosomal abnormalities associated with loss of 11q region of chromosome 13, which were associated with tumor progression and metastatic spread, were reported. Allelic deletions 11q13, 13q12—14, 10q and 1p were found in invasive pituitary adenomas. This information is to a greater degree related to prolactinomas and somatotropinomas rather than corticotropinomas. The lack of information on chromosomal disorders in corticotropinomas causes the need for further study in this direction [43—45].

Investigations of microRNA are promising with respect to prognostic factors of the biological behavior of corticotropinomas. MicroRNAs are non-coding endogenous RNAs regulating gene expression at the post-transcriptional level. MicroRNAs may act as a tumor gene suppressors or as prooncogenes. These proteins can be determined by quantitative real-time PCR and microarray techniques.
Various studies demonstrated both overexpression and hypoexpression of microRNA in ACTH-secreting pituitary adenomas. Reduced expression of miR-145, miR-21, and miR-141 was reported in corticotropinomas, which was associated with poor prognosis [43]. In somatotropinomas and prolactinomas, decreased expression of miR-15a and miR-16-1 correlated with tumor size as opposed to corticotropinomas [46]. F. Amaral et al. [43] revealed hypoexpression of miR-145, miR-21, miR-141, and let-7a in corticotropinomas compared to normal pituitary gland and found no relationship between the size of these adenomas and the results of neurosurgical treatment. Decreased expression of miR-141, which is associated with the development of CD remission after prostatectomy, exempted from this rule. Overexpression of a number of microRNAs, such as 122, 10b, 208a/b, and 592, which may be associated with tumorous progression of corticotropinoma [24, 47], was reported in the literature.

Proteomics and transcriptomics are among the most innovative methods to study various human diseases, including pituitary tumors. These methods are based on determining the extensive profile of proteins in various media (blood, tissues, etc.) using gel electrophoresis, mass spectrometry (for proteomics), and microarray studies (for transcriptomics). Transcriptomics and proteomics can detect a large number of protein compounds, facilitating understanding of carcinogenesis, and microarray studies (for transcriptomics).

These data can be used as markers of the biological behavior of pituitary adenomas [24].

As can be seen from the above, the knowledge on clinical presentation, histological structure, and immunophenotype required to assess the biological behavior of ACTH-secreting pituitary tumors, has been accumulated. However, the true proportion of typical and atypical corticotropinomas is not known so far. There are no results of long-term studies related to outcomes of neurosurgical treatment of corticotropinomas, depending on diagnostic categories of these tumors (typical and atypical adenomas). At the same time, the relationship between the histological structure of corticotropinomas, their immunophenotype, and outcome after prostatectomy is being studied. Results obtained by many international research teams have shown that functional activity of tumor cells (proliferative and antiproliferative processes), stromal component, and angiogenesis are of certain importance for understanding of the biological behavior of corticotropinomas. However, these data are disem bodied and there is no comprehensive understanding of these processes. In this regard, the molecular genetic aspects of corticotropinoma carcinogenesis is being extensively studies all over the world, which probably will enable discovering reliable predictors of poor prognosis of pituitary adenomas and, in particular, corticotropinomas, in the future.

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Commentary

Evaluation of biological behavior of pituitary adenomas, including corticotropinomas, is extremely important to find out the causes of pathogenesis and progression of pituitary tumors, as well as to develop effective methods of diagnosis and treatment of this complex and diverse group of tumors.

Until recently, pituitary adenomas were divided into acidophilic, basophilic, chromophobic, and mixed ones. However, this classification was of little importance for diagnosis of tumors, since there was no sufficient correlation with clinical presentation of the disease.

In 1995, E. Horvath and K. Kovacs proposed a modified classification based on morphological, immunohistochemical, and ultrastructural features of different types of adenomas. According to this classification, there are somatotropic, lactotropic, mammo-somatotropic, corticotropic, tireotropic, gonadotropic, plurihormonal, “silent”, and other types of adenomas.

The latter morphological classification of pituitary tumors has been revised by the WHO over 10 years ago (in 2004).

However, in recent years, numerous studies focusing on pituitary adenomas (including ACTH-secreting ones) were published, using modern morphological methods.

The authors analyzed a large bulk of modern literature on morphology and molecular biology of pituitary adenomas.

Interestingly, the article was written by prof. E.I. Marova, one of the pioneer researchers of Cushing's disease in our country, and candidate of medical sciences A.M. Lapshina, an expert in the modern morphological diagnosis of pituitary adenomas, which enabled comprehensive assessment of the results provided by laboratory and instrumental methods together with clinical presentation of the disease.

The review presents an interesting analysis of histological and immunohistochemical aspects of ACTH-secreting pituitary tumors compared to other morphological types of pituitary adenomas. Morphological classifications of pituitary adenomas and criteria of pituitary adenocarcinomas are shown. The authors demonstrated the possibilities of widely used histological and immunohistochemical diagnostic methods for pituitary adenomas, as well as the prospects of epigenetic research including the study of microRNA expression, proteomics, and transcriptomics.

This paper presents the best known biomarkers playing an important role in the pathogenesis of pituitary adenomas, in particular corticotropinomas. The article will be extremely useful for neurosurgeons, endocrinologists, and morphologists, who deal with the problem of pituitary adenomas. The data reported in this article can be taken as a basis for planning prospective studies, including the study of the morphological features of pituitary tumors with subsequent follow-up study and identifying the factors that play the most important role in the pathogenesis and biological behavior of tumors, including prediction of relapses.

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