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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.
High-Resolution 3D Time-of-Flight MR Angiography in Imaging of Lenticulostriate Arteries in Patients with Insular Gliomas


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Objective. To evaluate the effectiveness of high-resolution time-of-flight (3D-TOF) magnetic resonance angiography (MRA) in imaging the medial and lateral lenticulostriate arteries and to determine their relationship to the tumor edge in patients with insular gliomas. Materials and Methods. 3D-TOF MR angiography data were analyzed in 20 patients with primarily diagnosed cerebral gliomas involving the insula. All the patients underwent non-contrast enhanced 3D-TOF MR angiography. In six cases, 3D-TOF MRA was performed before and after contrast enhancement. Results. 3D-TOF angiography performed before intravenous contrast injection made it possible to visualize the medial lenticulostriate arteries in 19 patients (95% of all cases) and lateral lenticulostriate arteries in 18 patients (90% of all cases). Contrast-enhanced 3D-TOF angiography allows better imaging of both the proximal and distal segments of lenticulostriate arteries. Three variants of the relationship between the tumor and lenticulostriate arteries were identified, namely, variant I: the tumor grew over the arteries without displacing them in 2 (10%) cases; variant II: the tumor caused medial displacement of arteries without growing over them in 11 (55%) cases; variant III: the tumor partially grew over and displaced arteries in 2 (10%) cases. In 25% of cases (5 patients), the tumor was poorly visualized on 3D-TOF MR angiograms because their signal characteristics did not differ from those of the medulla (the tumor tissue was T1 isointense). As a result, it was impossible to determine the relationship between the tumor and lenticulostriate arteries. Conclusions. High-resolution time-of-flight MR angiography can be recommended for preoperative imaging of lenticulostriate arteries to plan the extent of neurosurgical resection in patients with glial tumors of the insular lobe.

Keywords: insular lobe gliomas, lenticulostriate arteries, 3D-TOF MR angiography.

Glial tumors account for up to 40—50% of all the primary cerebral tumors, with the significant number of them (25% of all the low-grade and 10% of high-grade malignant tumors) involving the insular lobe or originating from it [1].

The increase in the extent of the glioma resection has been reliably shown to directly correlate with the extension of patient’s life [2—4]. Yet, surgical treatment of gliomas of this localization remains one of the most challenging tasks of neurosurgery, which is related to the anatomic features of this brain region. The tumor often grows beyond the insular lobe, extending to the frontal and temporal lobes and affecting the anterior perforated substance along with perforating arteries in it. A surgeon has to work in the area surrounded by important opercular regions of the brain (especially in the dominant hemisphere) and penetrate into the insula between the branches of the M2 segment of the middle cerebral artery, whereas the lenticulostriate arteries (LSA), the basal ganglia they carry blood to, and the internal capsule are the medial resection border. All the above anatomic features make radical resection of a glioma without subsequent neurological deficit rather difficult.

As virtually all the severe postoperative complications in patients with insular gliomas are related to the damage to the LSA (permanent hemiparesis caused by ischemic lesion of the internal capsule) [5—9], preoperative detection of their intraparenchymatous growth and their location in relation to the tumor becomes especially important.

The goal of the study was to evaluate the effect of high-resolution time-of-flight (3D-TOF) magnetic resonance angiography (MRA) in imaging of the medial and lateral LSA and their relationship with the tumor edge in patients with insular gliomas.

Material and methods

The study involved 20 patients with primary insular lobe gliomas who had not been subjected to prior surgical treatment, chemotherapy, and radiation therapy. In all the cases, the T1-weighted scans showed no accumulation of Gd-containing contrast by the tumor. Magnetic resonance imaging (MRI) was performed according to the following protocol: T2 and T2-FLAIR-weighted images, diffusion-weighted T1 images before intravenous (i/v) contrast enhancement and T1 images after it. All the patients underwent non-contrast enhanced 3D-TOF MRA; in 6 cases the patients underwent it before and after contrast enhancement. 3D-TOF MRA was performed in the transverse plane using the gradient echo pulse sequence, with the following parameters: TR/19 ms, TE/1 ms, TE (out of phase)/3.4 ms, flip angle — 18°, FOV — 22 mm, the matrix — 640×352 mm, scan thickness — 1.2 mm; ZIP-1024, resolution 0.5×0.5×1.2 mm with subsequent reconstruction of
medial and lateral LSA in the maximal intensity projection (MIP) at a customized workstation. Non-contrast enhanced 3D-TOF MRA was performed for 14 (70%) patients; for 6 (30%) patients MRA was performed before and after contrast enhancement. The total duration of MRI was 25—30 min. The data of high-resolution 3D-TOF MRA before and after i/v contrasting were analyzed in order to estimate the degree of visualization of the medial and lateral LSA and to determine their relationship with the tumor tissue edge.

Results

According to the results obtained, high-resolution 3D-TOF MRA allowed detection of both medial and lateral LSA in the impaired brain hemisphere in most cases. The use of 3D-TOF MRA before i/v contrasting made it possible to visualize the medial LSA in 19 (95%) patients and lateral LSA in 18 (90%) patients. Small LSA branches were better visualized in the patients for whom 3D-TOF MRA was performed both before and after i/v contrasting compared to those for whom angiography was performed only before i/v contrasting. Contrast enhancement improved visualization of the most distal sections of those arteries. The entire course of the arteries was visualized more clearly, as well as the details of their location in relation to the tumor.

The major effect of this program is T1-weightedness; since only gliomas that did not accumulate Gd-containing contrast were included in the study (most gliomas affecting the insular lobe have a low degree of malignancy and do not accumulate contrast [1]), i/v contrasting did not improve tumor visualization in 3D-TOF MRA. This was the reason why we were able to determine the relationship of LSA and the tumor only for 15 (75%) patients, as the tumor tissue was hypointensive in the T1-weighted MRI. Tumor growth over the LSA without artery dislocation was revealed in 2 (10%) patients (Fig. 1b). In 11 (55%) cases, the LSA were displaced in the medial direction and were located along the medial edge of the tumor (Fig. 2b), while in 2 (10%) cases the tumor partly grew over and displaced the arteries (Fig. 3b).

Intraoperative confirmation of the 3D-TOF MRA data was clearly demonstrated in 15 cases. In 5 (25%) patients the tumor was poorly visualized in 3D-TOF MRA, as their signal characteristics did not differ from those of the medulla (the tumor tissue was T1 isointense). As a result, we were unable to determine the relationship between the tumor and the LSA, so the angiogram data were not clinically significant, as only artery dislocation was identified in the tumor growth zone, compared to the opposite side.

Postoperative 3D-TOF MRA performed for 6 patients confirmed the LSA intactness. Clinically the patients did not demonstrate any increase in the neurological deficit in the postoperative period.

Thus, three variants of the relationship between the tumor and the LSA were identified in the material under study: I — the tumor grew over the arteries without displacing them (Fig. 1b); II — the tumor caused medial displacement of arteries without growing over them (Fig. 2b); III— the tumor partially grew over and displaced the arteries (Fig. 3b).

Description of clinical cases

Clinical case 1. Growth of the tumor over the LSA (variant I)

A 22 year-old male: among the clinical manifestations, paroxysmal symptoms prevail presenting as generalized and partial seizures with oral automatism ("smacking"), loss of consciousness, and its gradual recovery. According to the brain MRI, a large cerebral tumor of the right insular, frontal, and temporal lobes was revealed (Yağarşılıg type 5B), not accumulating contrast and also proliferating to the anterior perforated substance (Fig. 1a, b). According to 3D-TOF MRA, the tumor tissue enveloped both the medial and lateral LSA (the arteries were included in the tumor edge rather than being located on it). The tumor was resected at the Burdenko Neurosurgical Institute. We were unable to visualize the proximal part of the arteries, as they were ingrown by the tumor and the risk of their damaging the arteries when attempting to isolate them from the tumor tissue was significant. The morphological diagnosis was grade II diffuse astrocytoma. No motor impairments were detected in the early postoperative period; however, the postoperative MRI identified the remaining part of the tumor in the area of the limen insulae and in the anterior perforated substance.

Clinical case 2. LSA without involvement into the tumor tissue (variant II)

A 35-year-old female: about two years before, the patient started to smell unfavorable odor for about 1—2 min, followed by seizures accompanied by loss of consciousness. The brain MRI revealed a tumor in the right insular lobe, spreading into the pole of the temporal lobe and the basal regions of the frontal lobe, not accumulating contrast (Yağarşılıg type 5A) (Fig. 2). The tumor was resected at the Burdenko Neurosurgical Institute. The morphological diagnosis was grade II diffuse astrocytoma. The patient’s neurological status after the surgery remained the same.

Clinical case 3. Impairment of the proximal zone of the LSA (variant III)

A 37-year-old female: the clinical symptoms included generalized and partial paroxysms with loss of consciousness for 30 min, feeling of numbness in the right arm and speech impairments. The brain MRI (Fig. 3a) revealed a brain tumor of the left insular lobe and the left temporal lobe (Yağarşılıg type 5A), which did not accumulate contrast. According to the 3D-TOF...
Fig. 1. Clinical case 1. Tumor growth around LSA (variant I).

a — preoperative T2-weighted MRI (4 scans at different levels): a large intracerebral tumor of the right insular, frontal, and temporal lobes (Yaşargil type 5B) with hyperintense signal; b — 3D-TOF reformatted MRA images after i/v contrast enhancement in the coronal and axial projections: tumor tissue involving the medial and lateral LSA (arrows) (the tumor edge is shown with red line); c — postoperative T2-weighted MRI (3 scans at different levels): subtotal resection of the tumor (the tumor remnants are shown in red); d — postoperative diffusion-weighted images (3 scans at different levels) without postoperative ischemic lesions in the surgical area.
Fig. 2. Clinical case 2: LSA not involved in tumor (variant II).

a — A T2-weighted MRI image (3 scans at different levels): a brain tumor of the right insular lobe insignificantly spreading to the temporal pole and the basal portions of the frontal lobe (Yagçılık type 5A) with hyperintense MR signal; b — 3D-TOF MRA (axial and frontal reformatted images): LSA position along the medial tumor edge (shown with a red line) not involved into the tumor tissue (arrow), a tumor with hypointense MR signal; c, d, e — 3D-TOF (c), as well as brain MRI 36 h after the surgery in T2-weighted (d) and diffusion images (e): intactness of LSA in subtotal resection of the tumor (an MR signal from the postoperative cavity in the remote tumor projection with a highly intensive signal as 3D-TOF due to the paramagnetic effect of methemoglobin; the DWI images show local hyperintense micro-zones along the resection edge — acute ischemia foci); f — an intraoperative image.

Footnote. M1 — the M1 segment of the middle cerebral artery. LSA — lenticulostriate arteries.

Fig. 2 is continued on the next page
MRA, the LSA were located along the medial edge of the tumor; however, some lateral arteries were included in the tumor tissue. Since the tumor was localized in the hemisphere dominant for speech, the patient was operated on using the ‘craniotomy in the conscious patient’ method. When the tumor was resected from the limen insulae and the adjacent anterior perforated substance, the lateral LSA was damaged in the region of its branching from the M1 segment. As a result, the patient stopped following motor instructions with her right limbs, due to which the tumor resection was stopped.

Motor impairments started in the early postoperative period (right hemiparesis up to grade 2). The diffusion MRI of the brain conducted on the first day after the surgery allowed visualization of ischemic impairment in the area of basal ganglia and the adjacent departments of the internal capsule on the left side.

Clinical case 4. Impairment of the distal section of LSA (variant I)

A 41-year-old male: the man suffered from complex partial seizures, which occurred up to 6 times per month. The brain MRI showed a cerebral tumor of the left insular and temporal lobes, which did not accumulate contrast (Yaşargil type 5A). Preoperative 3D-TOF MRA showed displacement of the LSA in the medial direction without tumor tissue ingrowth (variant I). We were able to identify these arteries and to preserve their proximal portion during the surgery at the stage of dissecting the M1 segment of the middle cerebral artery and extracting the tumor from limen insulae. However, two small arteries were damaged and subsequently coagulated at the final stage of the surgery (extraction of the medial part of the tumor mass, along which these arteries were located according to 3D-TOF MRA).

In the early postoperative period, the patient had right-sided hemiparesis (up to grade 3). Diffusion MRI of the brain performed within 24 h after the surgery showed ischemic lesions along the medial edge of the resected tumor bed and in the posterior limb of the internal capsule.

Discussion

Saving LSA remains one of the challenges in surgery of the insular lobe. Being branches of the M1 segment of the middle cerebral artery, these arteries perforate the central and lateral parts of the anterior perforated substance and supply blood to the basal ganglia and the internal capsule. Although the number of LSAs varies from 5 to 24 [10], occlusion even of one artery may result in extensive infarction in the area of subcortical ganglia and the internal capsule [11]. In most cases, due to the extensive effect caused by the tumor mass, LSAs get displaced in the medial direction to form an arch-like
Fig. 3. Clinical case 3: impairment of a proximal segment of LSA (variant III).

a — cerebral MRI (T2-weighted image) in the axial projection before surgery (3 scans at different levels): an intracerebral tumor of the left temporal-frontal area with hyperintense MR signal, b — functional MRI with mapping of speech areas: on the left — Wernicke center, the typical location (red color) and at a certain distance from the posterior pole of the tumor; c — 3D-TOF MRA (frontal reformatted images): medial LSA (white arrow) are located along the medial edge of the tumor (the edges of the tumor tissue are shown in red), lateral LSA (blue arrow) are partially involved into the tumor tissue; d — intraoperative image (the red arrow indicates the site of coagulation of the lateral LSA): LSA, anterior perforated substance, limen — limen insulae; e — postoperative diffusion MRI of the brain: an ischemic stroke in the projection of the posterior limb of the internal capsule (arrow).

Footnote. M1 and M2 — M1 segments of the middle cerebral artery.
bend along the medial edge of the tumor (Fig. 4b), which we observed in 11 (55%) cases.

LSA impairment is referred to as the main cause of persistent neurological deficit in virtually all the known studies devoted to the surgery of insular gliomas [5—9, 12]. Intraoperative tracking of the LSA is quite difficult, especially when the transcortical access to the insular lobe is used. A number of authors have offered to use a micro-Doppler sensor to ensure intraoperative identification of LSA localization; however, this method is not used in practice due to technical challenges it involves [11].

In order to identify the plane in which a LSA diverged, M. Yaşargil et al. [13], followed by F. Lang et al. [8] (advocates of the transylvanian approach to the insular lobe) suggested dissecting the horizontal portion of the Sylvian fissure as far as the first (counting from the approach) perforating artery diverging from the M1 segment of the middle cerebral artery. As a result, an essential landmark emerged: the vertical plane transecting the first lateral LSA, determining the medial border of the tumor resection.

In surgical practice, even in the case of maximal proximal dissection of the stem of the middle cerebral artery until the first lateral LSA diverges, it is very difficult to track the subsequent position of the arteries and the site of their inflow into the anterior perforated substance due to small diameter (about 1 mm) and variability of the number of arteries. Therefore, originally M. Yaşargil et al., followed by M. Simon et al. [15] and H. Duffau et al. [5], suggested leaving a small portion of the tumor mass in the area of the anterior perforated substance to prevent damage to the perforating arteries.

To estimate the LSA course, M. Yaşargil et al. [13] suggested preoperative carotid artery angiography for all the patients having impairment of the insular lobe. For the same purpose, H. Duffau et al. [5] used a non-invasive approach, CT angiography, for two patients in the series of cases they observed. However, the resolution power of the method proved to be insufficient for the task to be solved.

To reduce the probability of transecting the LSA during tumor resection, F. Lang et al. [8] performed MRI in standard modes before the operation and thoroughly analyzed the ratio of these arteries (the flow void effect in the T2-weighted image was the absence of signal from the arteries in this imaging, i.e. the arteries looked like black dots) and the tumor and planned the amount of surgical intervention accordingly.

Y. Moshel et al. [16] obtained interesting results by comparing preoperative MRI and carotid angiography. According to their findings, determining displacement of the LSA by the angiography results and overlapping these data on the preoperative MRI scans may be of help in predicting the degree of tumor invasion in the LSA. In accordance with this, the authors identified two types of insular tumors: the first type of tumors displaces the LSA medially, with LSA not involved into the tumor tissue and located on the border of the cerebral tissue and the tumor (the presence of a clear medial border of the tumor according to the T2-weighted MRI images is characteristic of this type); growth of the second type of tumors located both medially and laterally does not result in medial displacement of perforating arteries (these tumors normally do not have clear borders on T2-weighted MRI images). The authors arrived at a conclusion that, according to carotid angiography results, the patients having large tumors that are located more laterally than the LSA and cause displacement of the arteries in the medial direction proved to be the most suitable candidates for total resection of insular tumors without further development of neurological deficit.

In addition to CT angiography, 3D-TOF MRA is a non-invasive method allowing the position of the LSA in relation to the tumor tissue edge. According to R. Saito et al. [17], preoperative imaging of LSA allows one to reduce the risk of intraoperative damage to these structures and enhance the degree of tumor resection. However, the authors did not report the number of the patients involved in the study and only described three clinical cases of using the technique. We have not found any other studies analyzing the use of high-resolution MRA in imaging of medial and lateral LSAs in patients with insular gliomas (including intraoperative confirmation of the angiography results).

Our study demonstrated that performing high-resolution 3D-TOF MRA after i/v injection of Gd-containing contrast allowed imaging of both medial and lateral LSA in patients with insular gliomas in 100% cases, whereas angiography conducted before contrast enhancement revealed medial LSA in 95% of cases and lateral LSA in 90% of cases. In addition, contrast enhancement allows better imaging of both the proximal and distal segments of the LSA. High-resolution 3D-TOF MRA allowed one to clearly determine the ratio between LSA and insular gliomas not accumulating contrast in 75% of cases. In the remaining 25% of cases, 3D-TOF MRA did not allow imaging of a clear border between the brain tissue and the tumor tissue, thus making it impossible to detect the course of the LSA in relation to the tumor edge.

Thus, in cases with hypointensive T1-weighted images of gliomas, 3D-TOF MRA is a highly informative method of LSA identification with three possible variants of their location in relation to the tumor tissue.

However, the weak point of this study is the fact that we did not use 3DT2, 3DT2-FLAIR pulse sequences in our protocol of cerebral MRI, which did not allow us to compare them in 3D-TOF MRA. In the future, this may possibly solve the problem of the absence of signal differences between the brain tissue and the tumor tissue that is isointensive in the T1-weighted images (which was so rare and constituted ¼ of all the cases) but hyperintensive in the T2-weighted images.
Fig. 4. Clinical case 4: impairment of a distal segment of the LSA (variant I).

a — cerebral MRI (T2-weighted image, 4 scans at different levels) in the axial projection before surgery, a largely expanded tumor with hyperintense MR signal; b — 3D-TOF MRA (frontal reformatted images): imaging of LSA (white arrow) located along the medial edge of the tumor and displaced in the medial direction; c — intraoperative image (black arrows show the direction of blood flow along the M1 and LSA, white arrow shows the LSA); d — postoperative T2-weighted MRI of the brain (3 scans at different levels); e — postoperative diffusion MRI of the brain: ischemic lesions in the area adjacent to the posterior limb of the internal capsule.
Conclusions

High-resolution time-of-flight (3D-TOF) MRA may be recommended for preoperative imaging of lenticulostriate arteries in planning the volume of neurosurgical operations for patients with insular gliomas. Performed after contrast enhancement, 3DTOF MRA increases the chances of visualizing compressed distal lenticulostriate arteries, especially of their distal segments.

REFERENCES


Commentary

The problem of successful management of insular gliomas is related to the maximum reduction of traumatization of the adjacent functionally important structures and the LSA system, which are often included in the tissue of the infiltrative glial tumor of this localization.

Most researchers have pointed out the objective challenges associated with intraoperative identification of these arteries even in their thorough micro-preparation and if maximum proximal dissection of the stem of the middle cerebral artery until branching of the first LSA was performed. It is difficult to track down the further course of the arteries and the place of their inflow into the anterior perforated substance due to the variability of their number and the small (less than 1 mm) diameter. Therefore, preoperative refinement of the relationship between the tumor and the LSA system tract is essential for reducing the possible postoperative complications (ischemic lesions) and consequences such as aggravation of neurological deficit.

For this purpose, the authors used the new technique of 3D-TOF MRA; they have convincingly demonstrated its effectiveness by thoroughly analyzing the technique using sufficient clinical material. The images presented illustrate well the details of the microanatomic relationship between the LSA course and insular gliomas, as well as inclusion of the stems of the microvascular bed into the tumor tissue and other details that need to be taken into consideration by an operating surgeon during microsurgical intervention.

Four clinical cases are described, good discussion is provided, and the conclusion made substantiates the necessity of conducting 3D-TOF MRA after i/v injection of Gd-containing contrast agent.

The paper is innovative, interesting, and contains practically important information for neurosurgeons and neuroradiologists.

V.L. Puchkov (Moscow, Russia)
Blood—Brain Barrier Permeability in Healthy Rats and Rats with Experimental C6 Glioma after Fractionated Radiotherapy of the Brain

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Brain tumors are accompanied by blood-brain barrier (BBB) dysfunction. However, targeted drug delivery still remains difficult to achieve. Objective. To evaluate the effect of fractionated radiotherapy on permeability of the blood-brain barrier in healthy rats and rats with C6 glioma in vivo. Materials and Methods. An increase in BBB permeability in C6 glioma was assessed by dynamic MRI monitoring (glioma size before and after radiation therapy in combination with immunotherapy, n=30) and confocal microscopy (fluorescence imaging of tumor invasion boundaries in a dose-dependent experiment for the amount of injected antibodies). In healthy rats, BBB permeability to macromolecular substances (MMS) was assessed by ELISA (n=23, 192 plasma samples) and confocal microscopy (n=7). Results. It was shown that BBB permeability to biological macromolecules in blood—brain and brain—blood directions was increased after fractionated radiotherapy. Conclusion: Drug delivery to the brain can be improved using therapeutic doses of radiation treatment that affects the BBB and thus the risk of serious side effects that are often associated with drug dose can be minimized.

Keywords: glioma, blood-brain barrier in norm and pathology, fractionated radiotherapy.

The stability of the internal environment of the brain is normally ensured by the integrity of the blood—brain barrier (BBB). Brain tumors are accompanied by BBB dysfunction. However, targeted drug delivery still remains difficult to achieve. Accordingly, the efficacy of prescribed chemotherapy or immunotherapy in brain tumors is extremely low as opposed to treatment of tumors of internal organs. What is the reason for such selectivity?

In clinical practice, a temporary break of BBB is achieved in exceptional cases by systemic administration of osmotic diuretics (mannitol) and inflammatory mediators (bradykinin) [1—3]. There are recent data on positive results of the preliminary irradiation of brain tumors before chemotherapy, but the range of applied doses of fractionated radiotherapy is quite wide [4—6]. For example, most researchers [7—9] believe that radiation therapy doses of 20 to 30 Gy with fraction size of 2 Gy can be used to break the BBB without any side effects.

In the last decade, there is only fragmented information on the molecular changes in the cerebral endothelium, astroglial reaction, duration and timing of the opening of the blood—brain barrier during fractionated irradiation [10—15]. The problem of cognitive function status and quality of life of patients after a cycle of chemotherapy or radiotherapy accompanied by increased life expectancy still remains controversial and open question in modern neuro-oncology [16, 17]. As a result, the study of advisability of preventive radiation therapy before chemotherapy or immunotherapy for patients with brain tumors is important.

The objectives of the study included evaluation of temporal parameters of increase in BBB permeability to specific and non-specific macromolecular substances injected into the systemic blood circulation of healthy rats and rats with C6 glioma subjected to various doses of fractionated radiotherapy.

Materials and methods

Experimental animals and experimental design. The study was conducted on 60 Wistar rats. At the beginning of the experiment, the rats were 2 months old and weighed 200±20 g. Prior to the experiment, the animals were kept in laboratory vivarium in cages (8 animals in each cage) on a standard diet (not less than 2 weeks) with free access to water and normal light regime. Housing conditions for rats and all experimental procedures complied with international rules of animal handling (the European Community Directive 2010/63/EU of 24 September 2010 available at http://mslasa.ru/wp-content/uploads/Dir_2010_63_Rus-LASA2.pdf). Rats were randomized into 2 groups. Group 1 included animals with C6 glioma model (n=30), group 2 included intact animals (n=30). Each group was divided into three subgroups treated with radiotherapy: 1A (n=10), 1B (n=10), 1C (n=5) and 2A (n=10), 2B (n=15), 2C (n=5). Additionally, each group included two subgroups without radiotherapy (1d and 2d).
Regimen of the rat brain irradiation. Irradiation of the rat brain was performed on PRIMUS linear accelerator (Siemens, USA) at the Burdenko Neurosurgical Institute using 6 MV bremsstrahlung with a dose rate of 2 Gy/min. The distance from radiation source to the plane of the rats was 100 cm. Four rats were irradiated simultaneously. The rats were placed into a foam mold with their noses directed toward the center in such a way that they rested against the wall of the mold and field boundary defined based on a half-height of dose distribution passed behind the brain with a margin of 5 mm. This ensured irradiation of the whole brain in all rats. Square field size at isocenter was 140 mm. Solid water layer with a thickness of 20 mm was used to provide electronic balance. Radiation field penumbra, which was determined based on the dose drop from 80 to 20%, was reduced to 4 mm by means of specially designed 60 mm thick frame of Wood’s alloy. Irradiation was performed without general anesthesia. The rats were immobilized using restrainers (DecapiCones Braintree Scientific, Inc., USA). The animals were daily exposed to irradiation 5 times a week until a total dose of radiotherapy of 36 Gy was achieved (2 Gy × 18 fractions (groups 1A and 2A), 4 Gy × 9 fractions (groups 1b and 2b), 6 Gy × 6 fractions (groups 1c and 2c), and 0 Gy × 0 fractions (groups 1d and 2d)).

The experimental protocol to assess BBB permeability in rats exposed to irradiation (normal and with glioma). In group 1, changes in BBB permeability for MMSs during fractionated radiotherapy of C6 glioma was evaluated by monitoring of magnetic resonance imaging (MRI) (morphometry of glioma before and after radiotherapy in combination with immunotherapy, n = 30) and confocal microscopy (fluorescence imaging of tumor invasion boundaries in a dose-dependent experiment based on the amount of administered antibodies). In group 2 rats, BBB permeability to MMSs was assessed by ELISA (n = 23; 192 blood plasma samples) and confocal microscopy (n = 7).

Quantitative analysis of BBB permeability based on concentration level of glial fibrillar acidic protein (GFAP) in blood serum of rats exposed to irradiation by enzyme immunoassay (ELISA, Sandwich option). After the cycle of radiotherapy, 2 ml of the whole blood was sampled from the tail vein of each rat once per 7 days during 3 months. Blood corpuscles were sedimented by centrifugation. Plasma was collected and frozen at −80°C. Components for ELISA (PabGFAP, recGFAP, and MabGFAP) were obtained in the Laboratory of Immunochemistry of the Federal Medical Research Center of Psychiatry and Addiction Medicine of the Ministry of Health of the Russian Federation. Polystyrene plate was activated by MabGFAP (100 µl with concentration of 5 µg/ml) in 0.1 M bicarbonate buffer with pH 9.6 for 8 h at 4°C. The plate was washed for 3 times to remove the excess of MabGFAP and blood plasma samples containing the antigen (50 µl) were added followed by incubation at 20°C for 1 hour. After another triple washing, PabGFAP with dilution of 1:5000 was added to the plate and developed using a-rabbit-HRP with dilution of 1:200 (Goat antirabbit IgG-HRP, Sigma, USA). Antispecies antibodies were preincubated for 1 h with murine serum (1:200) to reduce their nonspecific adsorption. The reaction of the substrate mixture with 3,3′,5,5′-tetramethylbenzidine (Ready-to-use, Invitrogen, USA) was stopped by adding 0.1 N HCl. The numerical value of GFAP concentration was calculated based on the optical density using a calibration curve.

Qualitative analysis of BBB permeability based on accumulation of fluorescencely labeled monoclonal antibodies in the brain of rats exposed to irradiation (BBB permeability for MMSs). Specific and non-specific immunoglobulins (Ig) were labeled with Alexa fluorescent label with different wavelengths using the protocol provided by manufacturer (Invitrogen, USA). Antibodies to GFAP (PabGFAP, MabGFAP), VEGF and connexin-43 (Cx43) — MabVEGF, were obtained at the laboratory of immunochemistry of the Federal Medical Research Center of Psychiatry and Addiction Medicine of the Ministry of Health of the Russian Federation. Additionally, commercial nonspecific Ig (Sigma, USA) and antibodies to von Willebrand factor (vWF) (Abcam, USA) were purchased.

The rats were injected with Ig labeled with Alexa 660 fluorescent label through the femoral vein under general anesthesia. Accumulation of labeled antibodies in brain structures in vivo was evaluated using confocal laser microscopy. To this end, 24, 48 and 72 hours after administration of the labeled antibodies, rats underwent transaortic perfusion of 4% paraformaldehyde under deep anesthesia and decapitation. The brain was then removed and 150—200 microns thick sections were prepared. Sections were exposed in the solution with polyclonal anti-GFAP (astrocytes), anti-vWF (endothelial cells) and immunodeveloped with antispecies antibodies (InVitrogen, USA) to visualize cell structures with a positive signal of Alexa 660.

Analysis of degradation of MabGFAP and IgG covalently bound to Alexa Fluor 488 in the blood. Binding of IgG and MabGFAP to Alexa Fluor 488 was performed according to the manufacturer’s protocol (Invitrogen, USA). The fluorescence intensity was measured using VICTOR X3 Multilabel Plate Reader fluorometer in obtained samples with various dilutions. The labeled antibodies were diluted in blood plasma taking into account 5% loss of fluorescence. Incubation in blood plasma and sampling in 18, 24, 48 and 72 hours were performed followed by measuring the intensity of fluorescence in the sample. Centrifugation through a 30 kDa filter (Alexa Fluor 488 — 0.7 kDa) and measurement of flow through fluorescence intensity were carried out.

Statistical analysis. GFAP level was compared to the control using Dunnett’s parametric test. The data were
Results

Quantitative analysis of GFAP in plasma of group 2 rats subjected to fractionated irradiation was conducted in 23 rats. According to ELISA, GFAP level in the blood plasma increased 1.5—2-fold compared to the normal level. The highest values of protein level in rat serum were observed on 3—4th and 8—12th weeks. Six weeks after radiotherapy, GFAP levels returned to baseline normal values. On the 10th week, maximum GFAP plasma level was observed. No significant differences in plasma concentration of protein in the groups of rats that differ in a single dose of radiation therapy were detected (Fig. 1).

The study of BBB permeability to high molecular weight biomolecules in the blood—brain direction was conducted 2 and 10 weeks after completion of radiotherapy cycle, focusing on quantitative GFAP values obtained by enzyme immunoassay.

Given that increase in BBB permeability to biological macromolecules after radiation exposure may not be selective, it was important to differentiate between nonselective and selective accumulation of antibodies. For this purpose, specific and nonspecific Ig labeled with Alexa fluorescent label (Dye Alexa 488 absorb 495 nm, emit 519 nm; dye Alexa 660 absorb 663, emit 690 nm; Life Technologies Corporation, USA) were used in the experiment.

At the first stage, we evaluated accumulation of nonspecific Ig in the brain of rats after exposure in vivo. 24, 48 and 72 hours after injection into the systemic circulation in each experimental group (Fig. 2a, b). It was found that in 72 hours the signal from the fluorescence of non-specific Ig in the brain tissue almost disappeared, and occasionally preserved fluorescence was observed only in the vascular cavity (see Fig. 2b).

In addition, the experiment with injection of labeled non-specific Ig have shown that BBB can be permeable to substances with a weight of over 150 kDa in all radiotherapy options that we applied (2 Gy×18 fractions, 4 Gy×9 fractions, and 6 Gy×6 fractions). Based on previously published data on the studies of cognitive functions after radiotherapy and positive effects of the latter against gliomas, a single fraction used in rats at the second stage was not more than 4 Gy. Thus, the fluorescent signal was recorded only 72 hours after injection of specific antibodies to VEGF, GFAP, and Cx43.

Target antigens for fluorescence imaging in vivo were selected based on the quantity of protein synthesis in the nerve tissue, specificity, and availability. The level of GFAP expression in astrocytes increases in reactive gliosis. Cx43 is a membrane protein for homologous and heterologous gap junctions between astrocytes, endotheliocytes, and tumor cells [18—21]. Synthesis of the vascular endothelial growth factor (VEGF) increases in response to hypoxia and inflammatory processes, including those caused by radiation exposure [22].

According to the data of microscopy, BBB permeability to monoclonal antibodies was increased for a long time. Two weeks after fractionated radiotherapy, we recorded BBB permeability to labeled Ig independent of single-fraction dose value. Ten weeks after
radiotherapy, permeability to monoclonal antibodies has not changed.

An intense fluorescence signal was observed on the sections of the anterior and middle portions of the brain and cerebellum after injection of monoclonal anti-GFAP and anti-VEGF antibodies into the systemic circulation of rats and 72 h blood circulation. When analyzing accumulation of Alexa 488 labeled monoclonal anti-GFAP antibodies in vivo, rat brain slices were further exposed in solution with polyclonal antibodies to GFAP and developed using Anti-mouse Alexa 594 antispecies antibodies. According to the results of confocal microscopy on localization of monoclones and polyclones to GFAP, monoclonal anti-GFAP antibodies were accumulated in reactive astrocytes (Fig. 3).

To determine the species of the structural elements, where the fluorescence signal from anti-VEGF antibodies injected into the bloodstream of rats was recorded, brain slices were counterstained with antibodies to vWF and Mab2B6. Immunohistochemical results demonstrate selective accumulation of anti-VEGF antibodies in vWF- and AMVB1-positive cerebral endotheliocytes (Fig. 4, 5).

Thus, we have demonstrated that long-term increase in permeability of the blood brain barrier to MMSs was observed when the brain of healthy rats was exposed to fractionated radiotherapy.

Additional experiment for degradation of Alexa 660 labels covalently bound to antibodies in rat serum was conducted to ensure the reliability of the results on accumulation of labeled antibodies in the nervous tissue. When analyzing the intensity of fluorescence in various dilutions of labeled antibody preparations, linear relation between the fluorescence and sample dilution was observed (Fig. 6). The background value measured in the normal blood plasma of rats was 724.8±223.2.

The minimum detectable value was calculated as the five-fold background value and it was 4740. In order to detect a 5% loss of fluorescence of labeled antibodies during incubation in blood plasma, this value was taken to be 5%. Consequently, the fluorescence intensity in the final sample should be at least 94,802. After dilution in blood plasma, fluorescence intensity was 126,473.6±1,385 and 131,541.6±1,694 for Alexa 488 and MabGFAP labeled antibodies, respectively. Fluorescence intensity in plasma sampled in 18, 24, 48 and 72 hours decreased over time.

Thus, fluorescence intensity in 72 hours was 111,814±9,245 and 112,340±9,552 for Alexa 488 IgG and MabGFAP labeled antibodies, respectively. The decrease in the fluorescence was 11.6 and 14.6% compared to the initial value for Alexa 488 IgG and MabGFAP labeled antibodies, respectively (see Fig. 6, Table). After filtration of labeled antibody preparations through 30 kDa pore size filters, flow through fluorescence values were significantly reduced (size of labeled antibodies was greater than 150 kDa). Fluorescence intensity differed from the background value in 24, 48, and 72 h (see Table).

Thus, the fluorescence intensity in the flow through samples taken at various time periods after the beginning of incubation did not exceed the background level. This indicates that there is no low molecular weight fluorescent components up to 30 kDa, indicating that cleavage of the

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**Fig. 2.** Microscopy of accumulation of labeled IgG in sections of rat brain 72 hours after intravenous administration of IgG Alexa 660 (red fluorescence). Sections were additionally immunodeveloped ex vivo using MabVEGF + Anti-mouse Alexa 488 (vessels — green). Nuclei were counterstained with DAPI (blue).

a — survey microscopic picture of slices of the rat brain with glioma (scale bar — 10 mm), b — increasing microscopy resolution to 20 microns.
When assessing the improvement of BBB permeability in experimental glioma for diagnostic and therapeutic agents during radiotherapy, we relied on the results of radiotherapy in dose-dependent experiments: the higher the single-fraction dose, the more evident antineoplastic effect [27]. In the case of 6-day long irradiation with a single dose of 6 Gy, glioma size did not increase from the beginning of radiotherapy. However, rats died of side effects within 2—3 days after completion of the experiment. In the group of rats with radiotherapy schedule 4 Gy\(\times\)9 fractions, the survival after radiotherapy was 100% and efficacy against tumor growth was evident. However, a week later, tumor growth resumed and invasion into the surrounding tissues was so intensive that another week later rats died of intracranial dislocation (Fig. 7a—c).

When immunotherapy was added within a week after completion of irradiation, in particular with MabCx43, which previously demonstrated antitumor efficacy in monotherapy, we observed further inhibition of tumor growth (see Fig. 7) [27]. In this case, a single injection of 1 mg dose of antibodies resulted in increased lifespan of the animals up to 56 days. In the case of monotherapy with the same dosage, similar effect was observed when it was administered weekly.

In addition, the results of confocal microscopy study of brain slices with glioma are shown. Previously, not less than 500 µg of MabCx43 with covalently bound Alexa fluorescent label had to be injected into systemic circulation of a rat in vivo to visualize a peritumoral area. After radiotherapy (4 Gy\(\times\)9 fractions and 2 Gy\(\times\)18 fractions), administration of labeled antibodies at a dose of 40 µg enabled registering the fluorescence signal at the reactive astroglisis area (around glioma) (Fig. 8).

Summarizing the results, we can state that BBB permeability to diagnostic and therapeutic agents increases after fractionated radiotherapy.
Fig. 4. Analysis of accumulation of Alexa 660 labeled MabVEGF in the striatum of the rat brain 72 hours after intravenous administration of MabGFAP + Anti-mouse Alexa 488 (green fluorescence), MabVEGF + Alexa 660 (red). The slices were additionally immunodeveloped with PabvWF + Anti-rabbit Alexa 594 (purple). Nuclei were counterstained with DAPI (blue).

<table>
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<th>Incubation time of labeled Ig in serum, h</th>
<th>Specimens of fluorescently labeled specific and nonspecific Ig</th>
<th>Fluorescence intensity values, conventional units</th>
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**Discussion**

The problem of permeability of the blood—brain barrier to therapeutic and diagnostic agents is still relevant and it is being intensively studied by researchers and clinicians around the world. Previously, researchers used radioactive markers [23], MRI monitoring [24], immunohistochemistry [25], positron emission tomography, quantitative analysis of albumin [26], and other methods in their experiments to estimate the increase in BBB permeability caused by therapeutic doses in the radiotherapy of the brain. In individual cases, such studies are already being carried out on patients. Permeability has been shown to increase upon daily fractionation of 3 Gy until a total dose of 30 Gy in brain regions bordering the irradiation field. Increase was directly proportional to the dose of ionizing radiation [10]. Fractionation with a single daily dose of 2 Gy [27] is advisable to reduce long-term toxicity. Another study [12] showed that the fractionation dose of 2 Gy used to change BBB permeability can optimize the effect of chemotherapy. D. Qin et al. noticed that BBB
**Fig. 5.** Microscopy of accumulation of Alexa 660 labeled MabVEGF in slices of the rat brain 72 hours after intravenous administration (corpus callosum) of Mab286 + Anti-mouse488 (green fluorescence), PabGFAP + Anti-rabbit Alexa 594 (purple), and MabVEGF + Alexa 660 (red).

**Fig. 6.** Time history of fluorescence intensity of labeled antibody specimens.

- **a** — during incubation of labeled antibodies in the blood plasma;
- **b** — in different plasma dilutions.
permeability within and around a tumor is only 20% higher than that in the normal brain tissue [12]. However, despite the investigations in this field, the use of radiotherapy aimed at enhancing BBB permeability and efficacy of chemotherapy is still limited [7, 28].

The use of ionizing radiation in clinical practice is based on differences in radiation sensitivity of tumor and normal tissues [7, 28]. Alternative processes of damage and recovery arise upon exposure to ionizing radiation. Normal tissue recovers from radiation injury more rapidly and completely than tumors due to stable neurohumoral interaction with the host. Using these differences and managing them, one can achieve total destruction of the tumor, while preserving normal tissues. Moreover, adequately chosen dose fractionation can result in significantly higher damage to the tumor.

In Russia, in the case of radical treatment, irradiation with fractions of 1.8—2 Gy 5 times a week once a day to total doses that are determined by morphological structure of the tumor and tolerance of the normal tissue in the irradiation area (typically 60—70 Gy). Standard regimen of the remote fractionated radiation therapy include irradiation of the bed of the resected tumor (or the tumor itself) plus 2 cm around to a total focal dose of 55—60 Gy in 25 to 30 fractions (1.8—2.0 Gy per fraction) during 5—6 weeks. Abnormal signal area is detected using T2-weighted MRI (or FLAIR mode in case of benign gliomas) [7]. Besides the conventional radiotherapy regimen, other regimens of dose fractionation can be used in patients with brain tumors [7]. Concomitant chemoradiotherapy resulted in median survival of 14.6 months compared to 12.1 months in the group where only radiation treatment was used [7]. In patients with severe somatic status, in some cases, chemotherapy is not performed (radiotherapy is not indicated to patients with intracranial hypertension, until it is resolved).

The study of various regimens of combined chemotherapy and radiation therapy in patients with malignant gliomas is an important clinical problem. In our experimental study, we have shown that increased BBB permeability was observed after radiotherapy in rats with C6 glioma. In hospital environment, it can facilitate permeation of high concentrations of chemotherapeutic agents into the tumor. It was previously shown that in clinical practice the break through the BBB can be achieved in patients with brain lymphoma using bolus intra-arterial administration of mannitol [1].

Study of BBB permeability in hospital environment is possible due to monitoring of blood levels of various neurospecific proteins that are present in plasma at low

**Fig. 7. MRI view of the rat brain with C6 glioma after radiotherapy according to the schedule of 4 Gx9 days.**

a, b, c — the 1st, 7th and 14th days after radiotherapy and after radiotherapy according to the schedule of 4 Gx9 days followed by administration of MabCx43; d, e, f — the 1st, 7th and 14th days after the radiotherapy.
levels in health and significantly increase in CNS pathology due to increased BBB permeability. GFAP can play a role of such marker. Elevated level of GFAP is observed in experimental models of astrogliosis due to cryogenic brain injuries, stab wounds, experimental allergic encephalitis, hyperthermia, electric shock, toxic injuries, and upon exposure to ionizing radiation. Changes in GFAP expression are used for qualitative or quantitative assessment of the severity of brain injury, as well as in malignant tumors [22, 24, 25].

Increase in GFAP level in various brain structures and blood after a single exposure to γ-irradiation has been investigated by V.P. Chekhonin et al. [29]. Increased GFAP level in the blood plasma was observed, which is indicative of enhanced BBB permeability to neurospecific proteins in brain—blood direction. We repeated this experiment, exposing rats to the total irradiation of the entire body surface with a single dose of 30 Gy. In this experiment, we did not register the increase in BBB permeability to radiolabeled antibodies in blood—brain direction. In contrast to a single high-dose total irradiation of the brain, fractionated radiotherapy with small doses resulted in long-term increase in permeability of BBB capable of transmitting biological molecules with a molecular weight of 150 kDa.

Meanwhile, we have shown that the efficacy of fractionated radiotherapy of C6 glioma correlates with a single dose value [22]. The higher dose value results in faster inhibition of tumor growth. However, the number of side effects and the risk of rapid death of the animal also increases. There was virtually no increase in glioma volume upon irradiation with fractions of 4 Gy. However, tumor growth resumed at twice the speed after completion of irradiation [27, 31].

Neurophysiological tests on rats in the control group (without glioma) revealed cognitive deficit with all
radiotherapy options that we (2 Gy×18 fractions, 4 Gy×9 fractions, and 6 Gy×6 fractions). The severity of cognitive disorders increases with increase in a single fraction dose [22, 29, 30]. For this reason, in the studies of BBB permeability in initially healthy rats (no glioma), we selected fractionation regimens that were shown to be effective in rapid stabilization of C6 glioma volume without severe side effects, namely 4 Gy×6 fractions and long-term irradiation with low doses of 2 Gy×9 fractions [31].

It has been shown that prolonged fractionated irradiation of the brain with small doses leads to BBB opening in blood—brain and brain—blood directions in healthy rats and improves permeability in experimental glioma. Total irradiation of the rat brain resulted in increased BBB permeability to macromolecular substances in all brain regions. In the case of targeted systems, increase in BBB permeability was observed at the area of presentation of the relevant antigen (i.e. there is selectivity of accumulation). In particular, we have shown that there was accumulation of labeled anti-GFAP and anti-Cx43 antibodies at astrogliosis area in is selectivity of accumulation). In particular, we have selected fractionation regimens that were shown to be effective in rapid stabilization of C6 glioma volume without severe side effects, namely 4 Gy×6 fractions and long-term irradiation with low doses of 2 Gy×9 fractions [31].

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Stability of the internal environment of the brain is normally ensured by the integrity of the BBB. Brain tumors are accompanied by BBB dysfunction. However, targeted drug delivery still remains difficult to achieve.

The study was aimed at assessing the timing of increase in BBB permeability to macromolecular substances in vivo after fractionated radiotherapy. The irradiation of the rat brain was performed on the PRIMUS linear accelerator (Siemens, USA) at the Burdenko Neurosurgical Institute. Increase in BBB permeability in C6 glioma was assessed by dynamic MRI monitoring (glioma volume before and after radiation therapy in combination with immunotherapy; \( n=30 \)) and confocal microscopy (fluorescence imaging of the boundaries of tumor invasion in a dose-dependent experiment for the amount of administered antibodies). In healthy rats, BBB permeability to macromolecular substances was assessed by ELISA (\( n=23; 192 \) plasma samples) and confocal microscopy (\( n=7 \)). BBB permeability to biological macromolecules was shown to increase in blood—brain and brain—blood directions after fractionated radiotherapy. In addition, the conjugate stability during prolonged incubation in serum was assessed, i.e. the analysis of degradation of antibodies covalently bound to Alexa Fluor 488.

Commentary

The problem of BBB permeability to therapeutic and diagnostic agents is still relevant. Similar studies are conducted in the laboratories around the world, in rare cases these studies are conducted in patients [5, 6, 14, 19, 20]. It has been shown that permeability increases upon daily fractionation of 3 Gy at the brain areas bordering the irradiation field [14]. The researchers showed that labeled anti-GFAP and anti-Cx43 antibodies are accumulated at atrogliosis area in response to radiation exposure and managed to visualize the vessels of the cortex, hippocampus, and cerebellum after injection of labeled anti-VEGF antibodies. In combination therapy of experimental glioma, preliminary radiotherapy allowed reducing the dose of therapeutic antibodies by a factor of 2.

Thus, in case of the need for combination therapy of glioblastomas, BBB exposure to therapeutic doses of irradiation may improve the delivery of drugs to the brain and thereby minimize the risk of serious side effects associated mostly with drug dose.

In summary, it can be stated that the problem of crossing the barrier is a topical issue and solution of this problem has clear prospects of practical implementation.

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Preliminary Results of Chronic Intrathecal Therapy in the Treatment of Spastic Syndromes of Various Etiologies

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Objective. The method of chronic intrathecal infusion of lioresal (baclofen) and opioid analgesics can be effectively used in severe spastic parapareses and tetrapareses that are resistant to conservative treatment and treatment with botulinum toxin. The objective of this study is to evaluate the efficacy of chronic intrathecal therapy in the treatment of generalized spastic syndromes of various etiologies. Material and methods. We operated on 15 patients with generalized spastic syndrome resistant to botulinum toxin, including 8 patients with cerebral palsy, 5 patients with the sequelae of spinal cord injury, 1 patient with the sequelae of traumatic brain injury, and 1 patient with the sequelae of purulent epididymitis. The efficacy of surgical treatment was assessed on spasticity (Ashworth) scale and locomotion status (GMFM-88 and Arens) scales and subjected to statistical analysis. Results. In most cases, significant decrease in spastic syndrome was observed from 4.26±0.7 before the surgery to 1.8±0.67 after the surgery (p<0.004). Along with regression of spasticity, statistically significant positive dynamics of locomotor function was observed in 8 cases. Conclusion. Chronic intrathecal therapy results in statistically significant regression of spastic syndrome, increase in the range of active and passive motions, and improvement of the locomotor function.

Keywords: spasticity, chronic intrathecal therapy, baclofen pump.

Spasticity syndrome occurs in a number of severe neurological diseases, such as cerebral palsy (CP), multiple sclerosis, the sequelae of an acute cerebrovascular accident (CVA), and traumatic brain and spinal cord injuries. Spasticity leads to the limitation of the range of active and passive motions and complicates rehabilitation treatment [1—4].

In most cases, the capabilities of conservative treatment of spastic syndromes are limited. The use of neuromuscular blockade with botulinum toxin in patients with diffuse increase in muscle tone is ineffective in many muscle groups. Reduced sensitivity to drugs and occurrence of adverse effects of anti-spasmodic therapies necessitate more radical methods of treatment of spastic syndrome [1, 2].

Since the mid-twentieth century, destructive neurosurgical operations on the spinal cord and peripheral nerves, such as rhizotomy, neurotomy, and DREZ-operations, are widely used. However, despite the high efficacy, these interventions resulted in a number of complications, such as uncontrolled muscle weakness, dysfunction of pelvic organs, and pain syndrome. Destructive operations do not allow dosing and adjusting the level of muscle tone, causing additional difficulties in rehabilitation treatment [5—7]. Since the 1970s, the method of chronic electrical stimulation of the spinal cord was implemented to clinical practice. It was effectively used in patients with mild spastic paresis [8]. Reversible and manageable effect of action, which allows avoiding uncontrolled muscle weakness, is an important advantage of this method compared to destructive surgeries. However, experience has shown that chronic electrical stimulation of the spinal cord was not sufficiently effective in patients with high level of spasticity (4—5) [9].

Further development of neurosurgery and neuromodulation in the early 1980s led to development of new effective method of treatment of spastic syndrome, chronic intrathecal baclofen therapy (ITB) using implantable pumps. In 1984, R. Penn and J. Kroin first reported the successful treatment of spasticity using ITB [10]. Later on, a number of studies showing the efficacy of ITB in patients with multiple sclerosis and the sequelae of spinal cord injury have been published. In 1991, the report on the efficacy of administration of baclofen in CP patient was published, and as early as in 1993, the effectiveness of administration of ITB in treatment of spastic CP was confirmed [8, 11].

Currently, ITB is widely used to treat spastic syndromes of various etiologies.

Material and methods

The study group consisted of 15 patients, including 9 (60%) males and 6 (40%) females; mean age was 31.3±10.75 years in both groups (Table 1, 2). Spasticity was the result of CP in 8 (53%) patients, spinal cord injury in 5 (33%) patients; traumatic brain injury in 1 (7%) patient, and purulent epididymitis in 1 (7%) patient. Five (33%) patients had lower spastic paraparesis, and 10 (66%) patients had spastic tetraparesis. Three CP patients also had a hyperkinetic syndrome, 9 patients had pathological scissor legs with underlying spasticity in the hip adductor muscles, 8 patients had equinus foot with underlying spasticity in the lower leg triceps. In 7 cases, spasticity prevailed in the biceps and brachial muscle,
causing flexion contracture of the elbow. In one case, spasticity occurred in the triceps muscle of arm, which manifested as pathological extension contracture of the elbow. One patient had nocturnal motoric automatisms in the lower limbs with underlying lower spastic paraparesis.

Before the surgery, all patients received conservative medical treatment with centrally-acting muscle relaxants (baclofen, tizanidine). In all cases, the effect of the therapy was insufficient.

Nine patients underwent one to three courses of therapy with botulinum toxin before the surgery. In 3 cases, it had no effect; in 6 cases, good clinical effect was observed at the beginning of therapy, however, repeated blockades were noneffective. Six patients with tetraparesis were not treated with botulinum toxin in connection with diffuse spastic syndrome.

All patients were included in the study from 2008 to 2013. Follow-up period ranged 0.5 to 5 years. The following inclusion criteria were used:

1) high level of spasticity — 3 points and more;
2) resistance to conservative drug therapy;
3) resistance to physiotherapy and rehabilitation therapy;
4) incapability of orthopedic correction of contractures in the context of spastic syndrome;
5) positive results of baclofen screening test;

Exclusion criteria included:

1) severe deformities of the musculoskeletal system;
2) general contraindications to surgery and general anesthesia;
3) negative results of baclofen screening test;
4) pharmacoresistant convulsive disorders;
5) impossibility of regular refills of the pump for some reason or other (residence of a patient in outlying areas, economic problems).

The patients were preoperatively examined by a neurosurgeon, neurologist, physiotherapist, and orthopedist. In all muscle groups, the level of muscle tone was graded on the Ashworth scale between 1 and 5 points. The range of active and passive motions was also assessed, including video recording of standard motor tests. Locomotor status was assessed according to the normalized GMFM-88 scale in CP patients, and on the Arens scale in other patients. The same survey was conducted 6, 12, and 24 months after the surgery. Preoperative and postoperative values of the level of muscle tone and locomotion status were subjected to statistical analysis using Wilcoxon test; the value lower than 0.05 was considered statistically significant.

Positive baclofen screening test was of key importance for inclusion of patients in the study. Patients were hospitalized for 3—4 days to conduct the test. The test was carried out at the intensive care unit with obligatory insertion of peripheral venous catheter and monitoring of the heart rate, blood pressure, and oxygen saturation, as well as the capability of artificial lung ventilation, if necessary. All patients underwent lumbar puncture at L3—L4 under local anesthesia. The starting dose of lioresal (baclofen, Novartis Pharma) was 50 µg in all cases. Lioresal was diluted with liquor in the ratio of 1:1 and then injected intrathecally (slowly) during 1 minute. The screening test was considered to be positive, if decrease in muscle tone by one or more points on the Ashworth scale was observed within 12 hours after

Table 1. The results of surgical treatment of CP patients before and after surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>GMFM, % before</th>
<th>GMFM, % after</th>
<th>Tone before</th>
<th>Tone after</th>
<th>Age, years</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.</td>
<td>60</td>
<td>67</td>
<td>4</td>
<td>2</td>
<td>34</td>
<td>5 years</td>
</tr>
<tr>
<td>P.</td>
<td>33</td>
<td>35</td>
<td>5</td>
<td>3</td>
<td>38</td>
<td>21 months</td>
</tr>
<tr>
<td>Sh.</td>
<td>35</td>
<td>38</td>
<td>3</td>
<td>1</td>
<td>20</td>
<td>19 months</td>
</tr>
<tr>
<td>G.</td>
<td>30</td>
<td>40</td>
<td>4</td>
<td>2</td>
<td>32</td>
<td>16 months</td>
</tr>
<tr>
<td>K.</td>
<td>35</td>
<td>35</td>
<td>4</td>
<td>2</td>
<td>24</td>
<td>16 months</td>
</tr>
<tr>
<td>L.</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.</td>
<td>35</td>
<td>40</td>
<td>5</td>
<td>2</td>
<td>25</td>
<td>11 months</td>
</tr>
<tr>
<td>U.</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>25</td>
<td>9 months</td>
</tr>
</tbody>
</table>

Table 2. The results of surgical treatment of patients with spinal spasticity before and after surgery

<table>
<thead>
<tr>
<th>Name</th>
<th>Arens before</th>
<th>Arens after</th>
<th>Tone before</th>
<th>Tone after</th>
<th>Age, years</th>
<th>Follow up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sh.</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Ya.</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>47</td>
<td>18</td>
</tr>
<tr>
<td>K.</td>
<td>3</td>
<td>4</td>
<td>3 + automatisms in legs</td>
<td>1; suppression of automatisms</td>
<td>51</td>
<td>17</td>
</tr>
<tr>
<td>K.</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>B.</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>O.</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>L.</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>34</td>
<td>1</td>
</tr>
</tbody>
</table>
injection. When there was no convincing muscle tone dynamics, the test was repeated with 75 µg of lioresal on the next day. The maximum test dose was 100 µg. The patients were discharged on the following day after the test. In the case of a positive result, implantation of baclofen pump was recommended; in the case of a negative result, patients were advised to use alternative methods of surgical correction of spastic syndrome.

We implanted Codman Med-stream pump (Codman, USA) in 4 cases and Medtronic Synchromed 2 pump (Medtronic, USA) in 11 cases. The operation was carried out under endotracheal anesthesia in the right lateral decubitus position. Skin incised at the projection of L3—L4 spinous processes to implant the catheter. Puncture of the subarachnoid space was performed from an oblique paramedian approach to avoid inflection and compression of the catheter between the spinous processes (Fig. 1). Movement of the catheter was controlled radiographically using electron-optical converter (EOC). In patients with lower spastic paraparesis, catheter was moved to T7—T8 level, and in patients with spastic tetraparesis it was moved to C7—T1 level. Purse string suture was applied around the catheter at the exit from aponeurosis to prevent liquorrhea through the channel, and the catheter was fixed to the aponeurosis using special anchor. The pump was implanted into a pocket formed in the left hypochondrium (Fig. 2). In patients with thick layer of subcutaneous adipose tissue (11 cases), the pump was implanted subdermally, while in patients with thin layer of adipose tissue (4 cases) it was implanted subgaleally.

In all cases, the pump was fixed to the aponeurosis using sutures.

The initial concentration of lioresal was 500 pg/ml in all cases. In patients with high speed of intrathecal infusion, the concentration of the drug was then increased (from 1000 to 2000 pg/ml). The starting rate of intrathecal infusion depended upon the effective dose of lioresal in the screening test and amounted to 50 or 75 mg/day. Later on, the rate was daily increased by 15—20% of the total dose until a clinical effect was achieved. Initial lioresal titration time was 7—10 days.

All patients underwent postoperatively puncture of the pump pocket to prevent the formation of seroma, because the pocket could accumulate tissue fluid due to its relatively large size. Patients were discharged on the 10—14th day after the operation. They were informed of the date of the next refill, which was automatically calculates by the pump. The average frequency of refills ranges 3 to 5 per year. Disposable pump refill kit (US) that includes needles, tubing, and bacterial filter was used for refill in all cases. Refill procedure was carried out at the dressing room. First, the pump was scanned and the residual volume of the container was fixed. Further, filling port was punctured and the remaining lioresal (1—2 ml) was evacuated. The pump container was then refilled with a new dose (20 ml or 40 ml). Usually, lioresal with a concentration of 500 µg/ml was initially used, and only starting with 2—3rd refill, we used more concentrated formulation, 1000 and 2000 µg/ml, respectively.

**Results**

In most cases, significant postoperative decrease in spasticity according to the Ashworth scale was observed, from 4.26±0.7 before the surgery to 1.8±0.67 after the surgery ($p<0.004$) (Fig. 3).

In 6 cases, complete recovery of joint range of motions was observed during chronic intrathecal infusion after implantation of the baclofen pump. In the remaining 9 cases, there was only partial recovery of the range of motions due to fixed contractures in these patients. In most cases, we used intrathecal infusion in a simple continuous mode, providing a constant lioresal flow rate. The average intrathecal infusion rate was 214±90.6 µg/day. In one case, a flexible infusion mode was used (flex) that enabled changing the rate of intrathecal infusion during the day. Before the operation, this patient suffered from nocturnal motor automatism, which started at 23.00—23.30 and continued until 3.00—3.30 and was accompanied by painful muscle spasms, due to moderate spastic syndrome in the legs. They were the main reason
prevented from the muscle weakness in the legs in the morning.

In one case, the pump was removed in a 7-year-old patient with the spastic CP. The rate of intrathecal infusion was 100 µg/day within 3 days after baclofen pump implantation. As a result, a good clinical effect was observed, including the reduced muscle tone from 4 to 2 points, and increased range of active and passive motions of the upper and lower extremities. On the 4th day after surgery, the patient’s temperature rose to 38°C, and seroma occurred in the pump pocket. In this regard, the regimen of antibiotic therapy was adjusted, and seroma content was sampled for plating. Inoculated medium remained sterile within 7 days. Because of the continued fever response, meningitis was suspected. CSF samples were collected through the catheter port and through the lumbar puncture. Inoculated medium was sterile and cytosis level (within 90/3) did not allow verifying the diagnosis of meningitis. The pump was removed in 2 weeks due to persistent fever response and seroma relapses. Fever response completely regressed on the 2nd day after pump removal. Inoculation of catheter fragments and pump lavage did not result in flora growth. For this reason, this case is regarded as an allergic reaction to the implant.

Seroma in the pump pocket was observed in 3 patients. All of them resolved within 2 weeks after surgery against the background of punctures.

We assessed the dynamics of locomotor functions 6, 12, and 24 months after surgery. The positive dynamics of locomotor status was observed: from 34±14.56% (before surgery) to 37.85±16.58% (after surgery; p<0.008) on the GMFM-88 scale in 5 (62%) patients with cerebral spasticity (Fig. 4); from 1.43±1.5 (before surgery) to 1.85±1.67 (after surgery, p<0.007) on the Arens scale in 3 (43%) patients with spinal spasticity (Fig. 5). In the remaining 7 cases, no dynamics of locomotor status was observed despite the regress of spastic syndrome.

Discussion

Numerous studies proved high efficacy of ITB [12, 13], and it may be the treatment of choice in patients with spastic syndrome resistant to conservative treatment. At the same time, ITB presents some risk because of possible disorders of the system, resulting in either excessive or insufficient flow of the drug. The most common causes of insufficient drug flow are the problem with a catheter (twisting, bending, or migration), which can limit or completely stop the flow of lioresal to the cerebrospinal fluid. This leads to spastic syndrome relapse, and, in more severe cases, to multiple organ failure and even death [13—15].

Programming errors, as well as fluctuations in ambient pressure and temperature are the most common cause of drug overdose. Excessive injection of lioresal causes diffuse muscle weakness, somnolence, and
our results: improved functions was observed in 62% of patients. In approximately 50% of patients, which correlates with literature [18, 19], ITB leads to improvement of locomotor function to functional improvement. According to the literature, However, the reduction of spasticity does not always lead to improvement of spastic syndrome is to improve their motor function.

In some studies [17], an increased risk of scoliosis during ITB was also observed. Therefore, in patients with spinal deformities, this technique should be selected with care or abandoned in favor of alternative ones.

A significant factor limiting widespread use of ITB in clinical practice in the Russian Federation is the need for continued support of patients with implanted pumps. In particular, this applies to refills. As practice shows, an average of 3 to 5 refills per year per patient are required. Consumables include lioresal (1 to 8 vials per one refill) and charging set. Currently, there is no unified program of medical support of these patients in Russia. For this reason, in most cases, patients have to buy their supplies at their own expense. One refill costs 50 thousand rubles and more. Thus, the high cost of refills is a significant deterrent to widespread use of ITB method. It is also limited because of the high cost of operation. The amount of quotas allocated for these operations is small and can scarcely meet the demand. Annually, up to 6 thousand new cases of cerebral palsy, up to 10 thousand new cases of spinal cord injury, and more than 50 thousand cases of cerebral and spinal stroke occur. At least 10% of patients are refractory to conservative therapy and require neurosurgical treatment. Thus, the minimum annual need for ITB reaches 6—7 thousand pumps.

Given the need to support patients with implanted pumps, as well as the implantation of new ones, it can be expected that the need for lioresal will grow exponentially. Therefore, lioresal should be included to the GMFM list.

In addition, it is necessary to organize ITB support centers and deploy them both in Moscow and in regions. It is desirable that in the case of complications of ITB, the patient could be delivered within few hours. Given the area of our country, there should be at least 50 such centers.

The main objective of treatment of patients with spastic syndrome is to improve their motor function. However, the reduction of spasticity does not always lead to functional improvement. According to the literature [18, 19], ITB leads to improvement of locomotor function in approximately 50% of patients, which correlates with our results; improved functions was observed in 62% of patients with cerebral spasticity and in 43% patients with spinal spasticity.

Of course, the functional outcome depends on the initial severity of the disease. In patients who belong to level 5 on GMFM scale and 0—1 on the Arens scale, the main objective of the treatment is to facilitate nursing process, while in patients with GMFM level 3—4 and Arens level 2—3, the objective is to improve the functional result.

Y. Lazorthes et al. [20] mentioned high variability of effective therapeutic daily dose of lioresal, which was explained by the etiology of the disease, as well as individual differences in the metabolism of baclofen.

In our series of observations, we used relatively small daily doses of lioresal (214±90.6 µg/day). This is due to the fact that spastic syndrome was the dominating clinical manifestation in all patients, while the secondary dystonia and hyperkinetic syndrome require significantly higher doses [21].

In 15—20% of cases [20], “flexible” mode of lioresal infusion is indicated to patients, when the medication is injected at different rates throughout the day. This mode is mainly used in cases when spasticity increases:

1) at night, which causes sleep disorders;
2) during motor activity and physical exertion [22].

In our series of observations, there was a patient who had dynamic manifestations of spastic syndrome in the form of automated movements that occurred at night. Spastic syndrome was effectively arrested using sharp increase in the rate of intrathecal infusion in the evening and night hours.

In a number of studies [23], the development of detrusor-sphincter dyssynergia was observed during administration of ITB, which caused dysuria in the form of delayed urination. However, no cases of urinary dysfunction were observed in our studies.

### Conclusion

Chronic intrathecal therapy can be used in patients with generalized spastic syndromes in case of failure of conservative therapy and treatment with botulinum toxin. ITB results in statistically significant regression of spastic syndrome, increase in the range of active and passive motions, and improvement of locomotor functions.

A large organizational work is required to implement ITB method in clinical practice, including:

1) increase in the number of ITB quotas;
2) listing baclofen in the Additional pharmacological support list;
3) expanding the network of ITB support centers;
4) training of specialists.

This requires cooperative action of the Ministry of Health of the Russian Federation and clinics that use ITB method.
Locomotor impairment with underlying spastic syndrome leads to limitation of the range of active and passive motions, causes arrested development of locomotor function, and complicates formation of motor skills. Because of persistent muscle spasticity, myogenic and then fixed contractures occur, which significantly hampers rehabilitation. In patients with generalized spastic syndromes, covering many muscle groups, neurological intervention is considered to be the best treatment. In patients with spastic tetraparesis, implantation of baclofen pump is the most appropriate type of neurosurgical treatment, since this technique enables affecting the pathological muscle tone in the upper and lower extremities.

In this article, the authors present the results of chronic intrathecal therapy of 15 patients with spastic syndromes of various etiologies. The technique of preoperative selection of patients is discussed in detail, including such an important step as baclofen screening test, as well as the technique of pump implantation. Postoperative programming of patients is covered.

The article discusses the important issue of supporting patients with implanted pumps. The need for periodic refill of pumps and correction of intrathecal infusion parameters imposes additional duties on surgeons and requires establishing support centers for patients with implanted systems similar to those in the US and Europe. Intrathecal lioresal is not included in the list of free drugs, which results in substantial cost load on patients. It is necessary to include lioresal in the Additional pharmacological support list on the analogy of the botulinum toxin to achieve the widespread practical use of chronic intrathecal therapy.

Treatment of chronic neurogenic pain syndromes is another important problem of the chronic intrathecal therapy. There is a large group of patients who need chronic intrathecal morphine as the only actually effective method to relieve severe drug-resistant pain syndrome. The problem of supporting patients who receive chronic intrathecal infusion of morphine is even more acute than in patients with spasticity due to the fact that morphine is a controlled narcotic drug, which creates additional difficulties in filling.

In my opinion, it would be appropriate to compare the author’s own results with the literature data. It would also be good to analyze the main advantages and disadvantages, indications and contraindications for chronic intrathecal therapy in more detail on the basis of the literature. In order to improve the comprehensibility of the material, the authors should add the annexure to the article with scales and classifications used in the work (in particular, the description of Ashworth and GMFM scales), and provide the corresponding reference in the bibliography.

In conclusion, it should be noted that the article covers the problem of surgical treatment of patients with spastic syndrome resistant to botulinum toxin. For the moment, the study is highly relevant and it is of undoubted interest for neurosurgeons, neurologists, pediatricians, and rehabilitation specialists.

O.N. Dreval’ (Moscow, Russia)
Comprehensive Assessment of the Outcomes of Surgical Treatment of Patients with Metastatic Injuries of the Spine

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¹Burdenko Neurosurgical Institute, Moscow, Russia; ²Clinical Hospital No 1 at Administration of the President of the Russian Federation, Moscow, Russia

An increase in life expectancy affects the incidence rate of cancer. According to diverse sources, metastases in the spine are detected during autopsy in 30—90% of patients with a history of cancer. In Russian literature, there have been no in-depth studies of the quality of life in patients with various metastatic tumors of the spine who underwent surgical treatment, which determines the relevance of this study. **Objective.** The objective of the study was to demonstrate the need for implementing target setting in the combination treatment of patients with metastases in the spine as the main tool to identify the factors that adversely affect the patients’ quality of life. **Material and Methods.** The quality of life of 56 patients aged 16 to 81 years was assessed, including 26 males and 30 females. Of them, 26 patients underwent surgical treatment between 2002 and 2009, and 30 patients underwent surgical treatment between 2009 and 2014. Kidney cancer was a primary disease in 30.3% of patients, multiple myeloma was a primary disease in 23.1% of cases, and single cases of melanoma, thymoma, as well as metastases of tumors of the gastrointestinal tract, uterus, ovary, lung, prostate, pancreas, and the thyroid gland also occurred and amounted on the average to 3.5% (1.8 to 7.14%). The primary tumor site was not identified during cancer screening in 10.5% of cases. The quality of life of patients was studied using the EORTC QLQ-C30 scale. The patients were surveyed prior to the surgery and then 1, 3, 6 and 12 months after surgical treatment during 1 year or until death. Preoperative and postoperative contrast-enhanced spiral CT and MRI examinations were used to control the extent of decompression of neural structures. **Results.** On the basis of these findings, the authors identified the main factors affecting the quality of life of patients and formulated a range of treatment goals for patients with metastases in the spine. **Conclusions.** Surgical treatment has a positive effect on the quality of life in patients with metastases in the spine. However, it is not a key factor with regard to survival rate of these patients. Therefore, a decision on the possibility and necessity of surgical treatment should be taken both by the patient and oncologists of different specialties.

**Keywords:** metastatic tumors of the spine, quality of life, surgical treatment of metastases.

Epidemiological studies indicate an increase in the number of patients with cancer. This is correlated to the increased life expectancy, expansion of diagnosis methods, new effective treatment modes for cancer, and other factors. Literature data reveal the spine to be more often a target for metastasizing than the other bones of the skeleton in the case of malignant tumors [1]. Thus, according to various data [2], from 4 to 20% of all bone tumors are localized in the spine. Of them, 4.6% are primary bone tumors, and the others are metastases (those of breast, lung, or prostate cancer in most cases). More than 30% of these tumors cause neurological symptoms [3—7]. Pain, pelvic organ dysfunction, and sensory and movement disorders occur among them more often. The severity of these symptoms depends on the location, size, and histological features of a tumor. Undoubtedly, neurological symptoms affect the quality of life in these patients. According to R. Coleman et al. [8], the median survival time of patients with metastases in the spine is higher than that of patients with metastases in the liver.

These facts are the ground for surgical treatment of patients with bone metastases, especially of those with metastases in the spine.

Adoption of new intraoperative visualization technologies, a variety of stabilizing systems, bone cements, and blood-saving techniques has significantly improved the safety and quality of surgical interventions. However, it is important to realize that surgical treatment of patients with metastases in the spine is overwhelmingly palliative. In this regard, an important step in making decision for surgery is to determine its specific objectives, which may be also the basis for objective evaluation of the quality of treatment of these patients. Decision on surgical treatment of patients with metastases in the spine is held together with the patient and/or patient’s relatives. The oncologist, radiologist, and surgeon participate in this process. Main criteria for selecting patients for surgery include life span of a patient and the possibility to improve the condition of a patient with minimal surgical risk [9—13].

The need for surgical treatment to this day remains a matter of argument due to conflicting data on the long-term effectiveness of palliative surgery and due to the lack of accurate methods that could predict the life expectancy of these patients. In other words, one of the primary goals is aimed at identifying patients for surgical treatment that is known to result in bad outcome, but still is advisable in terms of the balance between risks and benefits. In our opinion, it was for situations such as this that formulating
clear goals for an individual patient can significantly objectify the decision on surgical treatment.

We have not found in Russian literature detailed studies devoted to treatment outcomes of patients who underwent surgical treatment for metastatic lesions of the spine, which emphasizes the relevance of this work.

### Material and Methods

A total of 56 patients (26 males and 30 females) with symptomatic tumors of the spine underwent surgical treatment at the Burdenko Neurosurgical Institute from January, 2002 to August, 2014. Of them, 26 patients underwent surgery during 2002—2009, and 30 patients underwent surgery during 2009—2014. The mean age of patients at the time of surgery was 57.4 years (range from 16 to 81 years). We established the presence of a metastatic tumor in the spine as the main criterion for patient selection, while patients with primary tumors of the spine, neurogenic tumors, and tumors of paravertebral soft tissues and adjacent organs, which infiltrated the vertebrae, were not included in the study. Data on the primary tumor foci are presented in Table 1.

Data analysis of histological studies of a primary tumor focus indicated the tumor to be a kidney cancer metastasis in 30.3% of cases; plasmacytoma was a primary disease in 23.1% of cases, and the primary tumor site was not identified during cancer screening in 10.5% of cases. Tumors of different histological nature, i.e., melanoma, thymoma, as well as metastases of tumors of the gastrointestinal tract, uterus, ovary, lung, prostate, pancreas, and the thyroid gland occurred in single cases (on average, 3.5% of cases; range 1.8—7.14 %). Three out of 56 patients had spinal surgery in the history; the other 53 were surgically naïve patients.

On admission, patients presented with complaints typical of compression syndrome (Table 2). Thus, according to our data, the main disease manifestations in the case of a metastatic spinal lesion at the stage of neurological symptoms in the spine, which emphasizes the relevance of this work.

### Surgical technique

In the study, main indications for surgical treatment were as follows:

1. Pain syndrome:
   - with no response to conventional technologies;
   - caused by local compression of neural structures;
   - caused by spinal deformity on the background of a pathological fracture;
   - spinal instability due to a pathological fracture of the vertebral body followed by compression of neural structures by a tumor in the spinal canal or outside of it.

The study did not include patients with severe kyphosis or scoliosis which were caused by pathological process and required orthopedic correction.

The objective of the surgery was either to eliminate or prevent compression of the spinal cord and its roots, and if necessary, to achieve stability of vertebral segments.

On admission to the hospital or at the stage of medical consultation, all patients were assessed using a range of prognostic scales (the Tomita, Takuhashi, Bauer, and Van der Linden scales) aimed at reasonable approach in predicting the mean survival time for each particular patient. The neurological status was determined on the Frankel scale, the performance status was evaluated on the Karnofsky scale, and the intensity of pain was assessed on the VAS pain scale.

Surgical treatment was planned using the WBB1 and SINS2 scales and was based on the data of neuroimaging techniques, namely magnetic resonance imaging (MRI), spiral computed tomography (spiral CT), and functional spondylograms.

The EORTC QLQ-C30 scale (version 3.0) was used as a tool for assessing the quality of life. The questionnaire of this scale is adapted for patients with cancer and is highly sensitive to the specific symptoms [14, 15]. This fact enabled assessing the severity of symptoms related to the pathology of the spine and separating them from

### Table 1. Primary tumor location in patients with metastases in the spine (n=56)

<table>
<thead>
<tr>
<th>Primary tumor site</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>17</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>3</td>
</tr>
<tr>
<td>Not identified</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>


2SINS (Spinal Instability Neoplastic Score) is a scale for assessing the degree of spinal instability and for planning the size of the stabilizing construction (Spinal instability neoplastic score: an analysis of tumor spread in a vertebra. The scale is titled by the first letters of the names of the authors: R. Biagini, J. Weinstein, and S. Boriani (Primary bone tumors of the spine. Terminology and surgical staging. Spine (Phila Pa 1976). 1997;22(9):1036-1044).
those of the underlying disease. The EORTC QLQ-C30 scale enables estimating social integration of patients, as well as significant aspects such as the physical health, emotional state, and the social status of a patient on the background of the disease. The questionnaire includes 30 items each with 4 possible answers. The answers are subsequently interpreted using a special table for determining the level of the principal criterion. The questionnaire includes a total of 7 criteria: physical health, emotional state, performance, cognitive function, financial issues, general health, and pain syndrome. The level of each particular criterion is measured in percentage terms [16]. Our patients completed the EORTC QLQ-C30 questionnaire before surgery and were surveyed during a year (at 1, 3, 6, and 12 months) after surgery or until death.

Table 2. Main clinical signs (complaints) of patients with metastases in the spine at admission (n=56)

<table>
<thead>
<tr>
<th>Clinical sign (complaint)</th>
<th>Incidence rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>80.0</td>
</tr>
<tr>
<td>Limb pain</td>
<td>20.0</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>37.0</td>
</tr>
<tr>
<td>Pelvic organ dysfunction</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Table 3. Assessment of the neurological disorders on the Frankel scale in patients prior to surgery

<table>
<thead>
<tr>
<th>Grade according to the scale</th>
<th>Neurological disorder</th>
<th>Patients (n=56)</th>
<th>number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Paraplegia</td>
<td>7</td>
<td>12,50</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Deep paraparesis without sensory disturbances or with partial sensory block</td>
<td>6</td>
<td>10,70</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Significant decrease in muscle tone</td>
<td>10</td>
<td>17,85</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Slight decrease in muscle tone</td>
<td>11</td>
<td>19,60</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Normal muscle tone</td>
<td>22</td>
<td>39,00</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. The incidence rate of symptoms detected during neurological examination of patients on admission

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients, n=56</th>
<th>number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local pain in the spine</td>
<td>54</td>
<td>96.4</td>
<td></td>
</tr>
<tr>
<td>Radicular syndrome</td>
<td>23</td>
<td>41.0</td>
<td></td>
</tr>
<tr>
<td>Monoparesis</td>
<td>7</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Local pain, paraparesis, pelvic organ dysfunction</td>
<td>11</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>Pelvic organ dysfunction</td>
<td>13</td>
<td>23.2</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Localization of metastatic tumors in the study population

<table>
<thead>
<tr>
<th>Part of the spine</th>
<th>Patients, n=56</th>
<th>number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spine</td>
<td>9</td>
<td>16.07</td>
<td></td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>22</td>
<td>39.28</td>
<td></td>
</tr>
<tr>
<td>Lumbosacral spine</td>
<td>21</td>
<td>37.50</td>
<td></td>
</tr>
<tr>
<td>Sacral spine</td>
<td>4</td>
<td>7.14</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Types of surgical interventions

<table>
<thead>
<tr>
<th>Type of surgical intervention</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct spinal angiography</td>
<td>4</td>
</tr>
<tr>
<td>Transcutaneous biopsy under CT control</td>
<td>4</td>
</tr>
<tr>
<td>Two-stage surgery*</td>
<td>56</td>
</tr>
<tr>
<td>Stabilization of spinal segments</td>
<td>1</td>
</tr>
<tr>
<td>Transcutaneous biopsy + vertebroplasty</td>
<td>2</td>
</tr>
<tr>
<td>Open biopsy + vertebroplasty</td>
<td>1</td>
</tr>
<tr>
<td>Surgical revision</td>
<td>4 (7 surgeries)</td>
</tr>
</tbody>
</table>

Footnote. * — stage I involved direct spinal angiography followed by either embolization using the adhesive compounds or occlusion using microcoils of afferent vessels feeding the tumor for reducing the volume of intraoperative blood loss; stage II involved decompression and stabilization of the spine.
Although the pain was assessed on the QLQ-C30 scale at various stages, we additionally controlled its intensity on the VAS pain scale before and after surgery.

Contrast-enhanced spiral CT and MRI were performed before and after surgery to control the extent of decompression of neural structures.

**Results**

Average length of hospital stay was 16.8 days (from 4 to 84 days). In the study, 56 patients underwent 82 surgical interventions (Table 6). It is significant to note that one patient was reoperated two years after the first surgery. In this case, the outcome was assessed after the second surgery without regard to the previous condition.

In our study, patients more often suffered a metastatic lesion of the lumbar and thoracic spine (Table 7). Analysis of the data on the number of vertebral segments involved in the pathological process (Table 8) reveals that only one vertebral segment was involved in most cases. In our study population, data on the parts of the spine subjected to surgical intervention is presented in Table 9.

Prediction of survival of patients according to the Takuhashi, Tomita, Bauer, and Van der Linden scales is presented in Table 10.

Data analysis of surgical approaches used (Table 11) revealed that the isolated posterior approach was performed in most cases. Importantly, two-stage surgery was performed in 16% of cases.

Forty-free patients underwent stabilization of spinal segments during surgeries involving the cervical (100% of

### Table 7. Localization of metastatic lesions in the study population (n=56)

<table>
<thead>
<tr>
<th>Part of the spine</th>
<th>Incidence rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spine</td>
<td>15.6</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>37.5</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>37.5</td>
</tr>
<tr>
<td>Sacral spine</td>
<td>9.4</td>
</tr>
</tbody>
</table>

### Table 8. Distribution of patients with regard to the number of spinal segments involved in the pathological process (n=56)

<table>
<thead>
<tr>
<th>Number of segments</th>
<th>Incidence rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.7</td>
</tr>
<tr>
<td>2</td>
<td>19.6</td>
</tr>
<tr>
<td>3 and more</td>
<td>10.7</td>
</tr>
<tr>
<td>More than 3 in different parts of the spine</td>
<td>9.0</td>
</tr>
</tbody>
</table>

### Table 9. Localization of surgical field (n=56)

<table>
<thead>
<tr>
<th>Surgical field</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniovertebral junction</td>
<td>6</td>
</tr>
<tr>
<td>Spine: Cervical spine</td>
<td>3</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>22</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>21</td>
</tr>
<tr>
<td>Sacral spine</td>
<td>4</td>
</tr>
</tbody>
</table>

**Fig. 1.** The pain syndrome dynamics according to the QLQ-C30 scale during 12 months of follow-up.

**Fig. 2.** T2-weighted MRI of the thoracic spine, sagittal view, signs of loss of the T5, T6 vertebral body height, myelopathy at the T5, T6 level.

**Fig. 3.** T2-weighted MRI of the thoracic spine, horizontal view, signs of a tumor of the T5, T6 vertebral bodies and of the 6th rib on the left side.

**Fig. 4.** T2-weighted MRI of the thoracic spine, sagittal view, signs of a tumor of the T5, T6 vertebral bodies and of the 6th rib on the left side.
Table 10. Assessment of patients on the Takuhashi, Tomita, Bauer, and Van der Linden scales predicting survival in patients (n=56)

<table>
<thead>
<tr>
<th>Score</th>
<th>Number of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Takuhashi scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 8</td>
<td>23</td>
<td>41.07</td>
</tr>
<tr>
<td>9—11</td>
<td>26</td>
<td>46.43</td>
</tr>
<tr>
<td>12—15</td>
<td>7</td>
<td>12.50</td>
</tr>
<tr>
<td><strong>Tomita scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2—3 (local control of the tumor)</td>
<td>22</td>
<td>39.28</td>
</tr>
<tr>
<td>4—5 (short-term local control of the tumor)</td>
<td>19</td>
<td>33.92</td>
</tr>
<tr>
<td>6—7 (short-term effect)</td>
<td>15</td>
<td>26.80</td>
</tr>
<tr>
<td><strong>Bauer scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0—1</td>
<td>12</td>
<td>21.42</td>
</tr>
<tr>
<td>2 (short-term effect)</td>
<td>13</td>
<td>23.23</td>
</tr>
<tr>
<td>3—4 (short-term relapse-free period)</td>
<td>31</td>
<td>55.35</td>
</tr>
<tr>
<td><strong>Van der Linden scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0—3 (Group A)</td>
<td>53</td>
<td>94.60</td>
</tr>
<tr>
<td>4—5 (Group B)</td>
<td>2</td>
<td>3.70</td>
</tr>
<tr>
<td>6 (Group C)</td>
<td>1</td>
<td>1.70</td>
</tr>
</tbody>
</table>

Table 11. Surgical approaches used for surgical decompression (n=56)

<table>
<thead>
<tr>
<th>Surgical approach</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients</td>
<td>%</td>
</tr>
<tr>
<td><strong>Isolated posterior (laminecctomy)</strong></td>
<td>45</td>
</tr>
<tr>
<td><strong>Anterior/anterolateral (corpectomy)</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Single-stage combined (spondylectomy)</strong></td>
<td>9</td>
</tr>
</tbody>
</table>
cases), lumbar (85.7%), and thoracic (77.2%) spine. No stabilization was performed in the surgical treatment for sacral tumors.

The dynamics of neurological symptoms according to the Frankel, Karnofsky, and VAS scales is presented in Table 12.

Monitoring of surgical treatment duration revealed that surgeries lasted from 30 to 660 min (275 min on average). The volume of blood loss in the study population ranged from 50 mL to 17 L (median volume of 2182 mL). Thirty-one patient required transfusion of blood components, and 8 patients needed their own erythrocyte reinfusion. In our view, it is of utmost importance that 83.3% of patients who underwent occlusion or embolization of afferent vessels during the first stage of surgical intervention also required transfusion of blood components during the surgery. The study revealed that the volume of intraoperative blood loss did not depend on the type of surgical approach.

The mean score of pain intensity according to the VAS pain scale was 7.2 before surgery. At discharge, all patients noted an improvement in pain intensity (average score of 2.7); preoperative score completely decreased in 6 patients. Then, the pain intensity was evaluated using the QLQ-C30 scale during follow-up (Fig. 1).

When assessing neurological status on the Frankel scale after surgery, only 10 patients reported clinical progress. The status of some patients changed on the Frankel scale: 1 patient upgraded from A to B, 2 upgraded from B to C, 4 upgraded from C to D, and 3 upgraded from C to E. Meanwhile, neurological deficit progressed in 5 patients. In addition, 1 patient downgraded from C to B, from D to C, and from E to D in one case each, and 2 patients downgraded from E to C. However, compared to the preoperative period, we observed a significant increase in the number of patients in group D (23% vs. preoperative 17.85%) on the background of a decreased number of patients in group C (17% before surgery vs. 12% after surgery).

None of 13 patients had the pelvic organ function restored during follow-up. Meanwhile, on the basis of the results of the EORTC QLQ-C30 questionnaire, we achieved a clear positive dynamics of the quality of life for all criteria. The most significant improvement was detected within the first 3 months after surgery. The dynamics of the quality of life on the QLQ-C30 scale during 12 months after surgery is presented in Fig. 2.

The most significant improvement was observed during evaluation of social adaptation (an increase of 50.4%), physical health scale (47.8%), global health status (45.7%), and physical functions (42.2%). Cognitive function and emotional state criteria improved by 21.7 and 21.5%, respectively.

By the end of the study, only 13 (23.2%) out of 56 patients underwent control examination; the date of death of 17 (30.4%) patients is known for certain. At the time of writing this article, we have failed to contact 26 (46.4%) patients operated on generally until 2009 (more than 5 years ago) or their relatives. Of these patients, 6 were examined within 1 month, 10 were examined within 3 months, 5 were examined within 6 months, and another 5 were examined within one year after surgery. Out of 25 patients operated on more than 5 years previously, 9 patients survived a period of 12 months after surgery, and 11 patients were alive at the time of writing this article.

Out of 56 patients, 9 (16.1%) were followed up no less than during 1 month, 18 (32.1%) were followed up

<table>
<thead>
<tr>
<th>Grade/score</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients</td>
<td>%</td>
</tr>
<tr>
<td><strong>Frankel scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>12.50</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>10.70</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>17.85</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>17.85</td>
</tr>
<tr>
<td>E</td>
<td>23</td>
<td>41.00</td>
</tr>
<tr>
<td><strong>Karnofsky scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>1</td>
<td>1.76</td>
</tr>
<tr>
<td>80</td>
<td>5</td>
<td>9.00</td>
</tr>
<tr>
<td>70</td>
<td>40</td>
<td>71.40</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>10.70</td>
</tr>
<tr>
<td>50</td>
<td>4</td>
<td>7.14</td>
</tr>
<tr>
<td>&lt;50</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>VAS scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1—5</td>
<td>8</td>
<td>14.1</td>
</tr>
<tr>
<td>5—10</td>
<td>48</td>
<td>85.9</td>
</tr>
</tbody>
</table>
### Table 13. The scale of achievement goals (the beginning)

<table>
<thead>
<tr>
<th>Achievement goals; grades</th>
<th>Goal 1 ( (w=10) ) Pain intensity reduction (do painkillers are needed or not?)</th>
<th>Goal 2 ( (w=9) ) Pain intensity reduction (according to the QLQ-C30 pain scale)</th>
<th>Goal 3 ( (w=8) ) Clinical effect (dynamics of neurological symptoms)</th>
<th>Goal 4 ( (w=5) ) Function (back pain or lower/upper limb pain) prevents to care for yourself</th>
<th>Goal 5 ( (w=6) ) Treatment satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>The worst treatment outcome ((-2))</td>
<td>Permanent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesser than expected treatment outcome ((-1))</td>
<td>Often</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected treatment outcome ((0))</td>
<td>Sometimes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than expected treatment outcome ((+1))</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal successful treatment outcome ((+2))</td>
<td>I do not remember when I last bought painkillers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Progression of neurological symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurological symptoms have not changed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction in symptoms of nervous tension without sensory, motor, and reflex changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No, but I try to be careful when moving</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial regression of neurological symptoms in the sensory, motor, and reflex domains</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No, I often forget about caution</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The effect of the treatment exceeded my expectations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complete regression of neurological symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No, and I forgot about the disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I recovered</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Achievement goals; grades</th>
<th>Goal 6 ( (w=2) ) Disability</th>
<th>Goal 7 ( (w=4) ) Functional activities at work</th>
<th>Goal 8 ( (w=3) ) Functional activities at home</th>
<th></th>
<th>Goal 9 ( (w=7) ) Period of temporary disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>The worst treatment outcome ((-2))</td>
<td>I do not work, since I am disabled</td>
<td>I am looking for another job due to the forced decrease in motor performance</td>
<td>I cannot do without assistance my daily domestic tasks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower than expected treatment outcome ((-1))</td>
<td>I am disabled with rights to work</td>
<td>I became less active; I try to limit physical activities at work (no lifting weights, to sit longer, etc.)</td>
<td>I perform limited domestic tasks, since some movements cause back pain or lower limb pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected treatment outcome ((0))</td>
<td>I returned to my previous job with temporarily sheltered employment</td>
<td>I am doing the previous scope of work (the same as before the illness)</td>
<td>I perform domestic tasks without assistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than expected treatment outcome ((+1))</td>
<td>I returned to my previous job and hold my previous position</td>
<td>I started to work more intensive than prior to illness</td>
<td>I perform domestic tasks and work in the garden without restrictions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal successful treatment outcome ((+2))</td>
<td>I move without fear, lift weights, and perform any task</td>
<td>The surgery does not affect my motor activities at work</td>
<td>I forgot about the disease; I engage in sports activities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
during 3 months, 7 (12.5%) were followed up within 6 months, and 19 (33.9%) were followed up during 1 year. Three (5.4%) operated patients did not survive a month after surgery and died from complications in the immediate postoperative period.

Among the complications that caused death, the blockage of the pulmonary artery branches (pulmonary embolism) occurred in 100% of cases and caused the development of sepsis, multiple organ failure, and death of patients on the 14th, 25th, and 8th day after surgery. Only 1 patient survived massive pulmonary embolism, which developed due to phlebothrombosis of the iliac vein and the inferior vena cava, and after sepsis caused by suppuration of a surgical wound, which leaved open for 39 days. A total of 6 cases of superficial surgical site infection were observed, including the aforementioned clinical case. In 5 patients, the existing serous cavity in soft tissues was suppurated on the background of superficial wound infection. Primary deep infection followed by necrosis of wound edges occurred in 1 patient after a multi-stage surgery and massive blood loss (up to 17 L).

The average follow-up was approximately 6 months (range from 0.25 to 48 months).

**Discussion**

The development of medical technologies contributes to significant progress in the treatment of cancer. The life expectancy of the population increases; doctors increasingly diagnose bone metastases, particularly in the spine. In this regard, one of the major problems in spinal surgery is the selection of patients with metastatic lesions of the spine for whom surgical treatment would be reasonable. When choosing the optimal therapeutic approach, doctors should assess now several variables: potential life expectancy; study objectives of the estimated surgery, its risks, and expected effectiveness.

Undoubtedly, it is extremely important to assess the effectiveness of alternative therapy (chemotherapy and radiosurgery). It should be noted that surgical treatment being compared to radiosurgery and chemotherapy was not an objective of the study, although it is extremely important. In 2004, P. Klimo et al. [1] conducted a meta-analysis that showed surgical treatment to enable faster decrease in pain intensity compared to radiosurgery. Then, the combination of surgery and radiotherapy was recognized to be even more effective.

According to our point of view, special attention should be given to the target setting approach for managing patients with this pathology. The range of targets is currently being developed to enable assessing the quality of treatment for patients with metastatic spinal lesions that is based on the assessment of goal achievement (Table 13).

A clinical case of the use of target setting in the treatment of a female patient with persistent spine cancer is presented below.

Five years before her admission, conventional X-ray revealed a tumor that involved the costovertebral angle and the 6th rib on the left side. The tumor was verified as plasmacytoma and resected. During the following 4.5 years, the patient felt well. However, 6 months prior to admission, the patient reported acute pain in the thoracic spine and gait disturbance after a fall from her own height. The patient gradually felt difficulty when walking and urinating. Contrast-enhanced MRI of the cervical and thoracic spine revealed a tumor of the 5th and 6th ribs that infiltrated the T5 and T6 vertebral bodies and spread into the spinal canal, the collapse of the T5 and T6 vertebral bodies, increasing kyphosis, and signs of spinal cord compression (Figs. 3 and 4). The patient started to receive combination chemotherapy and completed two courses prior to admission.

When examined, the patient showed symmetrical spastic lower limb paraparesis (score of 2 or 3; grade C according to the Frankel scale) and incomplete

<table>
<thead>
<tr>
<th>Index according to the scale</th>
<th>Index abbreviation</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status</td>
<td>QL2</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Physical health scale</td>
<td>PF2</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Physical functions</td>
<td>RF2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Emotional state</td>
<td>EF</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>CF</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Social adaptation</td>
<td>SF</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Symptoms</td>
<td>NV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>FA</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>NV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>PA</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory impairment</td>
<td>DY</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>SL</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>AP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>CO</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>DI</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Financial issues</td>
<td>FI</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
urinary retention as the pelvic organ dysfunction. The patient could not stand even with assistance; her muscle tone in the lower limbs was increased and conductive sensory disturbances from the T5 level on both sides were detected.

General oncologist, chemotherapist, radiologist, and neurosurgeon discussed the clinical case. Given the increasing neurological deficit, immediate surgery was indicated. However, given the diagnosis (heavy chain disease, the tumor of the T5 vertebral body, state after partial resection of the tumor), no radical surgery was planned. It was decided to modify chemotherapy and radiation therapy of the tumor spread area, to resect the T5 and T6 vertebral bodies, and to perform interbody stabilization at the T4–T7 level using a telescopic vertebral prosthesis and a side plate for decompressing the spinal cord and preventing the development of spinal deformity.

When discussing the treatment schedule with the patient, we found out that the target of the treatment was to restore the function of the lower extremities and to decrease the amount of painkillers which the patient was taking. She was aware that the purpose of the surgery was the spinal cord decompression and total tumor resection was not due to the absence of the growth dynamics after radiotherapy.

When assessing the state of the patient, we observed the severity of pain on the VAS pain scale corresponding to the score of 7 for the back pain and to the score of 6 for the lower leg pain. The results of survey according to the QLQ-C30 scale are presented in Table 14. The WBB and SINS scales were used for planning the surgical intervention. The score on the WBB (A, B, C, and D zones, 1—4 sectors; C and B zones, 1—8 sectors) and on the SINS scales was 12 in each case, which corresponds to severe spinal instability and deformity that require correction and stabilization of the supporting anterior column.

Given the fact that the tumor spread mainly in the area of vertebral bodies and compressed the spinal cord anteriorly, we chose the anterolateral approach to resect the tumor. Using transthoracic access with partial resection of the 5th and 6th ribs, we removed the T5–T6 vertebral bodies via curettage and hi-speed drill under the control of intraoperative CT and navigation system. After the spinal cord decompression, stabilization of the supporting anterior column was performed in the spinal canal using a telescopic vertebral prosthesis. The T4–T7 vertebral bodies were fixed using a plate and transcortical screws. The volume of blood loss did not exceed 700 mL. According to the data of neurophysiological intraoperative monitoring, no hemodynamic changes and a decrease in potentials were observed during surgery.

In the early postoperative period, the patient reported a significant improvement in her state: the pain regressed on the 2nd day, following which the patient was activated, became confident to stand on her own feet with assistance, and her normal urination recovered on the 10th day (residual urine volume was less than 100 mL). According to the control spiral CT of the cervical and thoracic spine, surgical complications were absent and the stabilizing construction was satisfactorily positioned (Figs. 5, 6). The patient’s condition improved at discharge on the 16th day after surgery.

On the whole, we achieved good treatment outcome for a given patient according to all scales (survey results according to the QLQ-C30 scale are presented in Table 14). Treatment outcome was also assessed using the aforementioned achievement goal scale (see Table 13). The patient filled in the table after surgery (anterior decompression and corporectomy of the T5 and T6 vertebrae). It turned out that we achieved the initial goal,
namely, the amount of painkillers was significantly reduced and the pain that the patient suffered before the surgery regressed completely (see Table 13: goals 1 and 2). With regard to restoring the lost function of limbs (goal 3), we also achieved improvements, i.e. function deficits partially regressed and leg muscle strength increased. Subjective evaluation was also high in regard to treatment satisfaction (goal 5). The patient settled in quite easily due to pain regression and due to recovered lost movements in her legs (goal 4).

We believe that studies of treatment outcomes of patients with metastatic spinal lesions must be sustained in perpetuity within the framework of the portal version of the Russian spine registry (http://www.itlaboratory.ru). Despite the organizational difficulties in this process concerning the need to give this work additional time, we consider it advisable to continue to cooperate with the N.N. Blokhin Russian Cancer Research Center.

Conclusion

Surgical treatment has a positive effect on the quality of life in patients with metastases in the spine, but is not of primary importance in terms of their survival. Therefore, firstly, the decision on the choice of surgical treatment for metastatic lesions of the spine should be based on a balanced assessment of its risks and potential benefits, as well as on a comparative assessment of the effectiveness of alternative treatment technologies (chemotherapy, radiosurgery, and their combinations); secondly, discussions on indications and usefulness of surgical treatment for patients with metastatic lesions of the spine should involve the patient (his relatives or his trusted persons), as well as the oncologist, radiologist, neurosurgeon, and chemotherapist.

On the basis of the analysis of multi-criteria assessment scales (EORTC QLQ-C30 and QLQ-C30), the results of this study suggest that surgical treatment enabled reducing the pain intensity (according to the VAS pain scale) and improving the quality of life of patients with metastatic lesions of the spine. In order to improve our research and receive a large amount of objective data on patients of this category, it is advisable to add data on the course of treatment and its outcomes in the prospective spine registry portal.

REFERENCES


Commentary

In the article, the authors summarize their experience in surgical treatment of patients with metastatic tumors of the spine. The authors give reasons for surgical indications and for the extent of the surgery. Details on patients’ pre- and postoperative status were given; methodologies and outcomes of surgical interventions were described. The proposed scale of goal achievement used for assessing treatment outcomes requires special attention.

In the article, the authors deeply analyzed oncological and functional outcomes of surgical treatment of severe group of patients with metastatic tumors of the spine; conclusions were drawn up and future prospects were indicated.

E. R. Musaev (Moscow, Russia)
Optimization of Treatment Outcomes in Patients with Segmental Instability in the Lumbar Spine Using a Minimally Invasive Spinal Fusion Technique

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Open transforaminal lumbar interbody fusion (TLIF), which is used to treat segmental instability, is associated with a significant paravertebral muscle and ligament injury. A new fusion technique was introduced to improve patients’ treatment outcomes. **Objective.** The objective of the study was to conduct a comparative analysis of the effectiveness of minimally invasive fusion technique and TLIF technique to improve treatment outcomes in patients with symptomatic degenerative lesions in the lumbar spine accompanied with moderate lumbar segmental instability. **Material and Methods.** The study involved 90 patients divided into 2 groups. Transforaminal interbody fusion using the pezo-T PEEK cage was performed in both groups after spinal canal reconstruction. In group 1 (n=45), conventional TLIF technique was performed by four-point transpedicular fixation using the CONMET system; in group 2 (n=45), the coflex-F rigid interspinous implant was used. Patients were followed up and treatment outcomes were assessed within approximately 24 months after surgery. **Results.** Intergroup comparison of pain intensity level on the visual analogue scale, the need for painkillers, and the quality of life according to the Oswestry Disability Index scale during the early postoperative period demonstrated significantly better outcomes in group 2 of patients due to a less severe operative trauma to the paravertebral soft tissues. Meanwhile, the formation of interbody bone block after 20—36 months was observed in 95% of patients in group 1 and in 94% of patients in group 2 (p>0.05). Postoperative complications occurred in 17.8% of patients in group 1 and in 2.2% of patients in group 2 (p<0.001). **Conclusion.** The use of rigid interspinous stabilization and transforaminal interbody fusion provides better clinical outcomes and fewer postoperative complications as compared to the TLIF technique in the case of similar X-ray pictures of the bone block formation in patients with moderate segmental instability of the lumbar spine, thus optimizing treatment outcomes in a given category of patients.

**Keywords:** segmental instability, lumbar spine, degenerative disc disease, TLIF, rigid interspinous fixation, transpedicular fixation, decompression.

More than 80% of the adult working-age population in the world experience low back pain [1]. The study of the causes of the vertebrogenic syndrome revealed that 80—90% of lumbosacral pain cases are associated with intervertebral disc pathology [2, 3], including segmental instability to be present in more than a half of the patients [4, 5].

The modern approach to eliminating clinically significant abnormal vertebral dislocation of one of the vertebra relative to another includes interbody cage placement and transpedicular fixation of an unstable spinal motion segment (SMS) [6, 7]. On the one hand, this type of fusion is associated with significant aggression against paravertebral soft tissue and damage to the muscular and ligamentous apparatus, which results in significant intracranial and paravertebral cicatricial and adhesive changes. The latter requires long period of healing and recovery and in some cases can worsen patients’ quality of life and affect their working capacity. [8] On the other hand, in the case of less radical surgical intervention, the remaining segmental instability is one of the common causes of recurrent pain in the postoperative period [2, 9].

The search for new technological solutions to improve the treatment outcomes of patients with symptomatic lumbar segmental instability is aimed at the development of surgical interventions for optimal decompression of neural structures and effective stabilization of the operated segment with minimal trauma to the surrounding tissues. A new fusion technique, comprising rigid interspinous stabilization with coflex-F implant (Paradigm Spine GmbH, Germany) and transforaminal interbody placement of pezo-T cage (Ulrich Medical GmbH, Germany), has been used at the Railway Clinical Hospital (Irkutsk, Russia) since 2010. This study focuses on the comparative evaluation of the results of the new technique and the conventional TLIF technique.

The objective of the study was to conduct a comparative analysis of the effectiveness of minimally invasive rigid stabilization technique and conventional transpedicular fixation for improving the treatment outcomes of patients with lumbar segmental instability.

**Material and Methods**

The study included 90 patients who meet the inclusion criteria, but not the exclusion criteria, and underwent surgery in 2010—2013. The study was approved by the Committee on Ethics of the Scientific Center of Re-

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con constructive and Restorative Surgery of the Siberian Branch of Russian Academy of Medical Sciences. The criteria for inclusion and exclusion in the study were indications and contraindications for minimally invasive interbody fusion for the treatment of the SMS instability.

Inclusion criteria were as follows:
— in the case of ineffective conventional treatment: prolonged or recurrent pain syndrome, permanent neurological deficit that may range from radiculoneuropathy to radiculopathy and is accompanied with peripheral nerve palsy;
— signs of moderate segmental instability (vertebrae are displaced relative to each other by more than 9 mm, but less than 15 mm) based on the results of functional radiography of the spine;
— grade I spondylolisthesis according to H. Meyerding (without spondylolysis);
— according to the data of neuroimaging, herniation or protrusion of the intervertebral disc followed by disc space or spinal canal narrowing that causes corresponding clinical symptoms.

Contraindications:
— central stenosis;
— grade II—IV spondylolisthesis according to H. Meyerding (with or without spondylolysis);
— severe comorbidity.

The patients were divided into two groups; both groups were subjected to transforaminal interbody fusion using the pezo-T polyetheretherketone (PEEK) cage. The inner cavity of the cage was filled with the bone autograft obtained from surgical approach. Group 1 \( (n=45) \) underwent four-point transpedicular fixation using the CONMET system (Russia) after the spinal canal reconstruction via laminectomy with unilateral or bilateral partial or total facetectomy; group 2 \( (n=45) \) underwent decompression via unilateral access using an original technique \([10]\) in the extent of unilateral partial facetectomy followed by stabilization with the coflex-F rigid interspinous implant.

After surgery, minimum follow-up was 8 months and maximum follow-up was 36 months (median time of 24 months). The following parameters were examined for a comparative analysis: gender, age, body mass index, technical features of surgical intervention (timing of surgery, blood loss, and the length of incision), activation time, duration of treatment at hospital, radiographic parameters for assessing the bone block formation capability (anteroposterior and lateral radiographs of the spine), and data of neuroimaging (1.5T MRI scanner, Siemens Magnetom Essenza, Germany). Clinical parameters were also assessed: the severity of pain according to the visual analog scale (VAS), the need for painkillers according to the number of nonsteroidal anti-inflammatory drug injections per day, and the quality of life in patients with low back pain according to the Oswestry index (ODI) \([2, 11]\).

All patients were operated on using original instruments by one surgical team, who had no social and economic interest in surgical outcomes.

Statistics and analytics application software (Microsoft Excel and Statistica 8) was used for statistical analysis of research results.

**Results**

In order to assess significant differences in samples, criteria of nonparametric statistics were used with the lower limit of validity of less than 0.05. The results were presented by median and interquartile range (IQR, 25th to 75th percentile). Statistically significant differences were detected in repeated measurements (3, 6, 12, and 24 months after surgery) with allowance for the Bonferroni correction \((p<2.5\%)\). Criteria of nonparametric statistical analysis included: the Mann—Whitney U test \((U)\) for intergroup comparisons, the Wilcoxon test \((W)\) for dependent samples, and the chi-square \((\chi^2)\) for binomial properties.

Medical background of the study population is presented in Table 1. During the intergroup comparison, no statistically significant differences were found \((p>0.05)\). Summary data on the duration of surgery, blood loss, the length of incision, time of patient’s activation and stay at hospital are presented in Table 2.

Comparative analysis revealed that the studied technical parameters were significantly lower in group 2 compared to group 1 \((p<0.05)\). This fact indicates that the interspinous stabilization with interbody fusion can be performed much faster (by 30% on average) and the access is less traumatic as compared to transpedicular fixation.

Analysis of the need for painkillers in the postoperative period was conducted (Fig. 1). A gradually decreased frequency of administration of painkillers in both study groups was noted; at the same time, total need for painkillers was significantly lower in group 2 over the time at hospital \((p_{M-U}=0.014)\). When analyzing the pain intensity level at the area of surgical site (Fig. 2), group 1 revealed significantly higher pain intensity level compared to group 2 \((p_{M-U}=0.035)\). Intergroup comparison of pain intensity according to the VAS scale (Fig. 3) revealed no statistically significant differences in the preoperative score \((p>0.05)\). At discharge and over the follow-up period (IQR within 2 years), significantly lower pain intensity level was detected in group 2 \((p<0.05)\), which may be associated with less severe operative trauma to paravertebral soft tissues.

Comparative evaluation of the quality of life in patients according to the ODI (see Fig. 3) revealed that preoperative values were comparable in both groups \((p>0.05)\); however, at discharge and during follow-up (mean time of 24 months), significantly higher scores of patients’ quality of life were observed in group 2 \((p<0.05)\), which may be associated with preserved functions of the
Table 1. Comparison of initial characteristics of the study population

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, IQR (25%—75%)</td>
<td>38 (32; 44)</td>
<td>39.5 (33; 49)</td>
<td>0.3</td>
</tr>
<tr>
<td>Male patients, n (%)</td>
<td>33 (73)</td>
<td>31 (69)</td>
<td>0.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8 (22.9; 29.1)</td>
<td>26.4 (23.5; 29.7)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 2. Comparison of two study groups according to surgical intervention technique and specificity of follow-up, IQR (25%—75%)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of surgery, min</td>
<td>205 (160; 220)</td>
<td>145 (115; 190)</td>
<td>0.01</td>
</tr>
<tr>
<td>Blood loss, mL</td>
<td>350 (300; 550)</td>
<td>50 (30; 100)</td>
<td>0.008</td>
</tr>
<tr>
<td>Length of incision, mm</td>
<td>100 (90; 150)</td>
<td>55 (45; 70)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Activation time, days</td>
<td>4 (3; 5)</td>
<td>2 (2; 3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Length of stay at hospital, days</td>
<td>13 (12; 15)</td>
<td>11 (9; 12)</td>
<td>0.04</td>
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Fig. 1. The need for painkillers in two groups of patients in the postoperative period.

caused 8 (17.8%) complications. Soft-tissue infection was identified due to hematoma infection symptoms (surgical wound drainage and local antibiotic therapy enabled the elimination of infection) in 3 cases; in 1 case, incorrect biomechanics restoration caused overload of facet joints at the adjacent surgical level and bilateral facet syndrome (after other possible causes of the pain syndrome had been excluded, facet joint radiofrequency denervation was performed resulting in complete regression of symptoms). In 2 patients, recurrent pain occurred due to disc herniation in segments adjacent to those subjected to fusion as the disc degeneration progressed and thus revision surgery was performed in the extent of microdiscectomy. In another 2 patients in the late postoperative period (4 and 7 months after surgery), recurrence of radicular symptoms was caused by the development of postoperative epidural fibrosis with no radiographic signs of foraminal and spinal stenosis, as well as with no signs of segmental instability according to the data of multislice computed tomography with myelography. In these cases, courses of conventional therapy significantly reduced the pain.

After interbody fusion and rigid interspinous stabilization, one (2.2%) complication was verified as a postoperative wound infection on the background of subcompensated type 2 diabetes. Local application of antiseptics and prolonged antibiotic course enabled to stop the inflammatory process.

Published materials of different authors that are devoted to lumbar spine fusion were compared with our results and these data are presented in Table 3.

Discussion

The relevance of studying new techniques of treatment for degenerative segmental spinal instability is linked to the lack of standard treatment approaches in the modern spine medicine, as well as to the efforts to improve the effectiveness of surgical interventions followed by negative outcomes in 3—20% of cases according to posterior muscular and ligamentous apparatus and less severe intracranial cicatricial and adhesive changes.

During follow-up (mean time of 24 months), control X-ray pictures of the spine in patients of both groups revealed no dislocation and migration of an implant, as well as no signs of segmental instability (Figs. 4, 5). The interbody bone block formation was detected in 86% of patients of group 1 and in 84% of patients in group 2 (p>0.05) 10—15 months after surgery and in 95% of patients in group 1 and in 94% of patients in group 2 (p>0.05) 20—36 months after surgery.

Sixty-two (69%) patients underwent control MRI of the lumbar spine 36 months after surgery. No data on the additional compression of the neural structures by structural elements were obtained. Signs of progressive degeneration of the segments adjacent to the operated ones were detected in 9 (20%) patients of group 1 (Figs. 6, 7).

No complications associated with the direct placement of stabilizing constructs were observed in both groups during the study. A comparative analysis of the number of postoperative complications revealed them to occur significantly often in group 1 compared to group 2 (p=0.0017). Interbody fusion and transpedicular fixation
different authors [8, 9]. These complications are associated with the insufficient bone block formation and with recurrence of neurological symptoms and pain syndrome after surgery. The objectification of indications for decompression and stabilization surgery, which is based on studying the severity of degeneration of the elements in the SMS [19], outcomes of surgical treatment, and mechanisms of fusion, cause decrease in the aforementioned adverse health consequences [7, 8]. It was found that the success of surgery for symptomatic instability in the SMS depends not only on decompression of neural and vascular structures in the intervertebral disc spaces and spinal canal, but also on the correctly performed orthopedic procedure, i.e. reconstruction, optimization, and stabilization of the space between osteocartilaginous structures of the spine [7, 20].

Significant intraoperative trauma, as well as a relatively high risk of early and late adverse effects in the form of recurrent spinal stenosis, insufficient bone block formation, and a false joint formation limits the use of open transpedicular fixation at the first signs of segmental instability [2, 15]. There is a direct correlation between the extent of resection of structural elements of the SMS and the development of postoperative instability in the case of spinal canal reconstruction via posterior approach [15, 20, 21]. In addition, insignificant presurgical spondylolisthesis, even in the case of insignificant surgical aggression towards elements of the posterior support complex (e.g., facetectomy) causes spondylolisthesis progression [22]. In such cases, there are indicators for stabilization procedure followed by rigid [12] or dynamic [14] transpedicular fixation via either open [13] or transcutaneous access [15] in most cases. A significant role in functional recovery of patients after open transpedicular fixation is played by the following factors: (1) severity of intraoperative injury of the muscular and ligamentous apparatus; (2) adequate correcting the abnormal segmental instability; (3) reliability of the bone block formation and its stability within prolonged period of time [7, 23].

Biomechanical studies [12—14, 24] have shown that a single transpedicular fixation in the case of unstable SMSs causes redistributed axial load on the pedicle screws, resulting in screw breakage (up to 10% of cases) and failure of the fixation system. In order to avoid such complications, the modern concept of rigid fixation combines interbody fusion and transpedicular fixation techniques and is regarded as “gold standard” of treatment for segmental spinal instability [14, 15].

The progression of the degenerative disc disease causes the interbody space to gradually sink and decrease in size and also the foraminal compression of neurovascular structures [5, 18]. Treatment options for correcting

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*Fig. 2. Dynamics of pain intensity at the surgical site area according to the VAS pain scale.*

*Fig. 3. Pain intensity dynamics on the VAS pain scale (0—100 mm) and quality of life dynamics according to ODI (0—100) in groups.*

_Footnote._ The values are given as median and IQR (25%—75%).
the height of interbody space include placement of osteoinductive or osteoconductive materials [14, 16]. A bone autograft was initially inserted into a disc space in order to form the fusion [23], but the tendency of an autograft to be resorbed and the high rate of pseudarthrosis caused the development and use of threaded cages [25, 26]. Interbody cage placement causes the disc space of indirect decompression of spinal nerve roots to widen by increasing the height of the intervertebral disc [5, 13]. This approach enabled quick and reliable fixation of the segment, increased the effectiveness of treatment, and reduced postoperative bed rest [24, 26, 27]. Invasiveness of bilateral placement of threaded cages and remaining risks of implant displacement after a wide decompression of the spinal canal [29, 30] required further search for interbody fusion options. The routine method uses a threadless bean-shaped cage, which is placed via unilateral

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**Fig. 4.** X-ray picture of the lumbosacral spine of a male patient P. (group 1), lateral view.

a — before surgery (sagittal translation of the SMS at the L4—L5 level, 11 mm);
b — 10 months after the L4—L5 interbody fusion using the pezo-T cage (Ulrich Medical GmbH, Germany) and four-point transpedicular fixation using the CONMET system (Russia): no sagittal translation in the SMS at the L4—L5 level and X-ray signs of full bone block formation.

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**Fig. 5.** X-ray picture of the lumbar spine of a female patient S. (group 2), lateral view.

a — before surgery (sagittal translation of the SMS at the L4—L5 level, 10 mm);
b — 9 months after the L4—L5 interbody fusion using the pezo-T cage (Ulrich Medical GmbH, Germany) and rigid interspinous stabilization using the coflex-F cage (Paradigm Spine GmbH, Germany): no sagittal translation in the SMS at the L4—L5 level and X-ray signs of full bone block formation.

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**Fig. 6.** MRI of the lumbar spine of a male patient P. (group 1), sagittal view.

a — before surgery (sequestered disc herniation at the L4—L5 level);
b — 20 months after the L4—L5 interbody fusion using the pezo-T cage (Ulrich Medical GmbH, Germany) and four-point transpedicular fixation using the CONMET system (Russia): no MRI-based signs of progressive degeneration in the SMS adjacent to the surgical site.

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**Fig. 7.** MRI of the lumbar spine in female patient S. (group 2), sagittal view.

a — before surgery (fragmented disc herniation the L4—L5 level);
b — 19 months after the L4—L5 interbody fusion using the pezo-T cage (Ulrich Medical GmbH, Germany) and rigid interspinous stabilization using the coflex-F cage (Paradigm Spine GmbH, Germany): no MRI-based signs of progressive degeneration in the SMS adjacent to the surgical site.
transforaminal access. PEEK cages became particularly popular due to a number of physical and chemical features, such as full biocompatibility, absence of cytotoxic and mutagenic effects, and parameters in biomechanics similar to those of a bone [31, 32].

Treatment outcomes of patients with posterior interbody stabilization are various. The technique of bilateral interbody fusion using cages that is combined with transpedicular fixation contributes to the formation of a bone block in 90% of cases, with good treatment outcomes amounting to 67% [33, 34]. In 1985, the search for a less traumatic posterior interbody fusion technique lead Blume [16] to develop the unilateral transforaminal technique that was followed by transpedicular access with placement of a bean-shaped cage into the intervertebral disc space.

The presented series of our observations showed a middle parts of disc spaces without kyphosis development [2] as well as allows restricting the SMS movement in sagittal plane [39]. The question whether to use interspinous implants or not remains unresolved. There is a large variety of indications for their use: spinal stenosis [38], initial instability in the SMS or preventive measures after discectomy [40], degenerative facet disease [42], degenerative spondylolisthesis [41]. Contraindications to the interspinous stabilization are regarded as follows: grade II—I degenerative spondylolisthesis, patients older than 70 years of age, signs of osteoporosis, and vertebral body fractures [37, 39].

No data on using both the interbody fusion and rigid interspinous stabilization for the treatment of patients with segmental instability in the lumbosacral spine were found in the specialized literature.

The presented series of our observations showed a stabilization technique using rigid interspinous implant placement to result in comparable clinical outcomes between levels of pain intensity and quality of life and the data of other published studies analyzing posterior lumbar interbody fusion (see Table 3).

Compared to the TLIF technique, the advantages of rigid interbody fusion with interspinous stabilization in the case of moderate abnormalities in spatial relationships in the SMS (translation of vertebrae relative to each other in sagittal plane according to the data of functional radiography of the spine, from 9 to 15 mm) are as follows:

1. less traumatic surgical approach with remaining optimal visualization of the spinal canal structures;

![Insert Table Here]

**Footnote.** * — M±m, ** — M (min—max), *** — IQR (25%—75%); TPF — transpedicular fixation, ISS — interspinous stabilization.
(2) simple rigid interspinous implant placement with minimum number of supplementary surgical instruments;
(3) effective unstable segment fixation and high incidence of bone block formation followed by fewer postoperative complications.

Conclusion
Treatment of symptomatic lumbosacral degenerative disc disease combined with moderate segmental instability by means of the surgical technique using both rigid interspinous stabilization and transforaminal interbody fusion enables to achieve better clinical outcomes and causes fewer postoperative complications compared to conventional TLIF in case of similar X-ray results of the bone block formation.

Thus, the minimally invasive stabilization technique enabled to optimize the outcomes of surgical treatment of patients in a given category.

This study was supported by grants of the President of the Russian Federation, MD-6662.2012.7 and SP-156.2013.4.

REFERENCES

The presented article is devoted to the topical issue — the treatment of degenerative disc diseases in the lumbosacral spine. At present, surgeons are familiar with a variety of surgical techniques developed for the treatment of this group of diseases. Despite the strict indications for all techniques, we should admit that occasionally we still use creativity in selecting the optimal surgical treatment. The article is a prime example of this.

It is no secret that implants, a part of which is intended to form the fusion, are used intraoperatively in some cases. The concept of this approach is that the pain caused by excessive segment movements regresses when the segment is fixed. Different technologies have been developed to stabilize spinal segments; the “gold standard” is regarded to be the 360° fusion. In this article, the authors propose for achieving this goal to use a combination of interspinous implant, which is positioned by the manufacturing company as a device for rigid stabilization, and an interbody cage made in Germany. Transpedicular stabilization using domestic system and interbody stabilization using cages made in Germany are compared.

All patients were divided into two equal groups of 45 patients. It should be noted that patients were also divided according to the extent and technique of neural structure decompression: decompression using unilateral approach was performed in group 2. The authors compared a complex of signs (duration of surgery, length of incision, blood loss, patient’s activation time, length of stay at hospital, etc.). Cumulative analysis of these indicators shows the advantages of combination technique with rigid interbody implant and interbody cage placement. Group 1 of patients who underwent transpedicular fixation combined with interbody fusion showed 17.8% incidence rate of complications, whereas this index reached 2.2% in group 2. From the perspective of case-based medicine, this study is near the base of the pyramid, which reflects the general state of affairs in the medical periodical literature. The article includes a number of inaccuracies, in particular, the authors said: “All patients were operated on using original instruments by one surgical team, who had no social and economic interest in surgical outcomes”. The interest in the treatment outcome certainly must be present.

Despite some comments, the study should be recognized as new, interesting, and worthy to be published in the journal; however, in my opinion, it is reasonable to conduct such researches not only within a single clinic, but also using the Spine Registry.

A.G. Nazarenko (Moscow, Russia)
Features of Nosocomial Meningitis in Patients of a Neurosurgical Critical Care Unit

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Burdenko Neurosurgical Institute, Moscow, Russia

We report the results of a prospective study on the development of bacterial meningitis in postoperative complicated patients of a neurosurgical critical care unit for the period of 2010—2014.

The aim of this study is to determine the incidence rate and risk factors of nosocomial meningitis in postoperative complicated patients. Material and methods. Disease complications requiring stay in the neurosurgical critical care unit for more than 48 h were observed in 1,153 (14.3%) patients. The data of these patients were systematized and added to the database. Results. Nosocomial meningitis (NM) developed in 146 patients, which accounted for 12.6±1.0% (CI, 10.74—14.66). The meningitis patients were characterized by a longer stay in the critical care unit (CCU), prolonged mechanical ventilation, the need for central venous access, and invasive monitoring of systemic hemodynamics as well as longer antibacterial therapy. The frequency of invasive monitoring of intracranial pressure had a similar effect in groups of patients with and without NM. The NM patients were more often detected with bloodstream infections (14.8% vs. 4.9%; p<0.000), respiratory tract infections (55% vs. 35.6%; p<0.000), and urinary tract infections (56.4% vs. 30.9%; p<0.000). The following significant differences were observed between the group of NM patients and the control group: more frequent use of external ventricular drainage (72.5% vs. 26.1%, respectively; p<0.000), a higher number of reoperations (64.7% vs. 36.3%, respectively; p<0.000), and a longer total operating room stay (417.3 min vs. 337.5 min, respectively; p<0.000). The etiology was identified in 61.0±4.0% of NM cases. CoNS (33.0%) and Acinetobacter baumannii (21.3%) were the main pathogens isolated from the cerebrospinal fluid. The mortality in the patients with meningitis was 31.5±3.8%. Conclusion. External ventricular drainage, repeated surgery, long-term stay in the operating room as well as infections of a different localization may be considered as the risk factors for developing nosocomial meningitis in neurological patients in a CCU.

Keywords: nosocomial meningitis, risk factors, CCU, prospective observation.

Health-care-associated nosocomial infections (NIs) are a major concern for the current health service since they result in ancillary diseases, increased mortality, longer treatment, and higher cost of therapy [1—3].

Because of objective reasons, the NI incidence rate in patients in critical care units (CCUs) accounts for 20—25%, which is significantly higher compared to that in other hospital departments [4]. The main risk factors include more frequent use of invasive devices and procedures, immediate severity of the condition of patients in a CCU and the extent of organ injury, immune status impairment in patients in critical conditions, and the need for extensive use of antibiotic therapy facilitating selection of multidrug-resistant pathogens — causative NI agents [2, 5, 6].

The features of health care to patients with neurosurgical pathology include the abolishment of the brain protective barriers during surgical interventions, longer surgery duration as well as use of invasive neuromonitoring techniques. The rate of infectious complications of the central nervous system (CNS) in CCU patients is expectedly different from that in patients at general surgical hospitals.

An epidemiological survey conducted at the Critical Care Department of the Burdenko Neurosurgical Institute in 2009 revealed that meningitis ranks third after lower respiratory tract infections (LRTIs) and urinary tract infections (UTIs) in the structure of NIs.

According to the literature data [7—11], the major risk factors of nosocomial meningitis include intraventricular hemorrhage, craniotomy, wound liquorrhea, and duration of neurosurgery and external ventricular drainage, with a significantly increased risk of infection after five days of drain use. Ventriculoperitoneal shunting, use of an intracranial pressure (ICP) sensor, and repeated surgery also play an important role [11].

The aim of this study is to determine the incidence rate of NMs and their clinical and epidemiological features in patients of a neurosurgical critical care unit.

Material and Methods

The study was conducted at the Neurosurgical Critical Care Department (NCCD) of the Burdenko Neurosurgical Institute from October 2010 to January 2014. The prospective study included all patients with stay in the CCU of more than 48 h. The features of somatic and neurological status of patients, signs of infection (systemic inflammatory response), and risk factors (external ventricular drain, ICP sensor, mechanical ventilation, central venous catheter, etc.) were recorded each day [3].
The results were added to a specifically developed database integrated into an electronic medical record of a patient. CNS infections (CNSIs) were diagnosed based on conventional Definitions of Nosocomial Infections developed by the United States Centers for Disease Control [12].

A total of 8,062 patients were hospitalized to the NCCD over the studied period. A complicated course of disease requiring stay in the CCU for longer than 48 h was observed in 1,153 (14.3%) patients. The information on these patients was systematized and included in the database. The clinical diagnosis of meningitis was made in 146 patients, which accounted for 12.6±1.0% (CI, 10.74—14.66). The diagnostic criteria included neutrophilic cytosis (number of cells in a counting chamber) of more than 150/3, the cerebrospinal fluid (CSF) glucose level of more than 50% of blood glucose, the presence of a CSF pathogen, signs of the systemic inflammatory response syndrome (SIRS), meningeal symptoms, and negative dynamics in the neurological status [12].

The age of meningitis patients ranged from 4 months to 88 years (the mean age was 37.6 years). The proportion of pediatric patients (under 18 years) was similar both in the NM group and in the control group.

Most of the meningitis patients were characterized by the supratentorial localization of the pathological process (72.8±3.7%). The posterior cranial fossa was affected in 20.4% of the examined patients. Spread of the pathological process to the supratentorial and subtentorial regions was observed in 5.4% of the patients, and the spinal level (thoracic spine) was affected only in 1.4% of the meningitis patients (Fig. 1).

The structure of neurosurgical pathologies in the meningitis patients included tumors of a various localization — 67.3%, traumatic brain injuries (TBIs) — 13.6%, and arterial aneurysms and cerebral arteriovenous malformations (AVMs) — 11.6% (Fig. 2). The proportion of patients with acute TBI in both groups was comparable.

According to the severity of the general condition at the time of admission to the Burdenko Neurosurgical Institute, the distribution of patients was as follows: 34 (23.1%) patients had the maximum grade of disability (score of 40 and lower by the Karnofsky scale) and 92 patients (62.6%) were in the compensated condition. The Charlson comorbidity index [13] reflecting comorbid somatic conditions and age was used to estimate the long-term prognosis in patients. In the NM patients, the index ranged from 0 to 10, with the mean of 3.

139 patients underwent surgery (94.6±1.9%). Brain tumors of different localizations were resected in 90 (64.7%) patients, with 1 patient having a combination of a tumor process and a vascular disease (multiple arterial aneurysms). Resection of AVM and clipping of intracranial aneurysms were carried out in 12 (8.6%) patients. Decompressive craniotomy as the primary surgical intervention (mainly in the case of TBI) was made in 6.5% of cases. Endoscopic, endovascular, and shunt surgeries were less common in the meningitis patients (Fig. 3).

The structure of complications at the NCCD was dominated by wound liquorrhea (34±3.9%), wound edge diastasis (17.7±3.1), and hematomas in the surgical field; the last required surgical wound revision in 18 patients (12.2±2.7%).

The duration of stay of the meningitis patients in the CCU varied from 1 to 167 days (mean of 40 bed-days), with 57 patients (38.8±4.0%) being re-admitted to the CCU.

The data were processed by means of parametric and nonparametric statistics, analysis of variance, and contingency tables usually using Statistica v.6 software and a set of programmes based on a book by S. Glants Medicobiological Statistical Data [14].

**Results and Discussion**

Over 3 years, the rate of meningitis in the group of complicated neurosurgical patients was 12.6±1.0% (CI, 10.74—14.66), and the mortality in the meningitis patients was 31.5±3.8%.

The etiology of meningitis was identified in 89 (61.0±4.0%) of 146 cases. The absolute number of isolated pathogens (gram-positive, gram-negative, and fungi of the genus *Candida*) in patients with meningitis of the identified etiology was 103 (Table). The prevailing pathogens in the study were gram-positive cocci, including coagulase-negative staphylococci (CoNS) (33.0±4.6% of the total pathogen number), as well as
Analysis of the NM group and the control group revealed that the mean age (37.6 years) of patients with CNS infection was significantly lower than that of patients without CNS infection (42.4 years). In the group of patients without meningitis, the distribution by gender was about the same in contrast to the patients with meningitis among whom males reliably predominated. The Charlson index was lower in the NM group compared to the control group (score of 3 vs. 3.4, respectively). The meningitis patients were characterized by a longer stay at the NCCD (by 22.9 days), prolonged mechanical ventilation (by 21.4 days), the need for central venous access (by 24.5 days), urinary catheterization, feeding through a nasogastric tube as well as a longer course of antibacterial therapy (by 20.1 days). In the group of NM patients, noninvasive monitoring of systemic hemodynamics was used more frequently (42.2%) compared to the group without NM (29.7%; \( p<0.003 \)).

The frequency of ICP monitoring was similar in the two groups of patients. The meningitis patients in comparison with patients without meningitis were more often detected with bloodstream infections (14.8% vs. 4.9%, respectively; \( p<0.000 \)), respiratory tract infections (55% vs. 35.6%, respectively; \( p<0.000 \)), and urinary system infections (56.4% vs. 30.9%, respectively; \( p<0.000 \)). There were statistically significant differences between the NM group and the control group: more frequent use of external ventricular drainage (72.5 and 26.1%, respectively; \( p<0.000 \)); the number of repeated surgeries (64.7 and 36.3%, respectively; \( p<0.000 \)); total operating room stay (417.3 and 337.5 min, respectively; \( p<0.000 \)).

Thus, the risk factors of NM may be tentatively classified into internal and external factors. The internal factors include: age, gender, severity of the patient's condition at the time of neurosurgical disease manifestation, and the nature of the disease. The main external risk factors, according to the literature data [7—11, 15], include external ventricular drainage, shunt surgery, liquorrhea, use of a ICP sensor, and repeated surgery.

In this study, the meningitis patients were characterized by a younger age (despite that the proportion of children in the two groups was not statistically different) and a low Charlson comorbidity index, which may indirectly indicate less comorbid pathology in these patients. These data are consistent with the data of foreign studies on NM [16]. Furthermore, the meningitis patients stayed longer at the NCCD, required the use of appropriate invasive devices (including prolonged mechanical ventilation), and significantly more often underwent neurosurgical interventions (external drainage and repeated surgery). It is remarkable that we did not observe a convincing impact of invasive ICP monitoring on the rate of meningitis.

Thus, the external risk factors were proved to prevail in the etiology of NM in patients of the NCCD, which may indicate the exogenous nature of infection. The gram-negative bacteria (32.0±4.6%). In this case, the proportion of \textit{Acinetobacter baumannii} as an etiologic NM agent was 21.3±4.0%.
Structure of pathogens isolated from patients with purulent meningitis

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Absolute number of pathogens, n=103</th>
<th>%±m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gr(+)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNS</td>
<td>41</td>
<td>39.8±4.8</td>
</tr>
<tr>
<td><strong>including</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>23</td>
<td>22.3±4.1</td>
</tr>
<tr>
<td><em>Streptococcus spp.</em></td>
<td>3</td>
<td>2.9±1.7</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>4</td>
<td>3.9±1.9</td>
</tr>
<tr>
<td><strong>Gr (−)</strong></td>
<td>60</td>
<td>58.2±4.9</td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>33</td>
<td>32.0±4.6</td>
</tr>
<tr>
<td><strong>including</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>16</td>
<td>15.5±3.6</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>7</td>
<td>6.8±2.5</td>
</tr>
<tr>
<td><em>S. marcescens</em></td>
<td>4</td>
<td>3.9±1.9</td>
</tr>
<tr>
<td><em>M. morganii</em></td>
<td>3</td>
<td>2.9±1.7</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>2</td>
<td>1.9±1.4</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>1</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td><strong>Nonfermenting gram-negative bacteria</strong></td>
<td>27</td>
<td>26.2±4.3</td>
</tr>
<tr>
<td><strong>including</strong></td>
<td></td>
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</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>22</td>
<td>21.3±4.0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>5</td>
<td>4.8±2.1</td>
</tr>
<tr>
<td><strong>Candida albicans</strong></td>
<td>2</td>
<td>1.9±1.4</td>
</tr>
</tbody>
</table>

presence of infections of a different localization may be considered as an additional factor contributing to the severity of condition of patients with meningitis.

**Conclusion**

Meningitides in neurosurgery are a serious problem leading to longer treatment, an increased need in antibacterial drugs, and an unfavorable disease prognosis. The risk factors of NM in patients in the CCU may include external ventricular drainage, repeated surgery, long-term stay in the operating room as well as infections of a different localization.

**REFERENCES**


The article analyzes the effect of internal (age, gender, and initial severity of the patient’s state) and external (external ventricular drainage, shunting surgery, craniotomy, liquorrhea, and repeated neurosurgical intervention) risk factors on the rate of nosocomial meningitis in patients of the neurosurgical critical care department. The external risk factors were found to dominate, which indicates predominantly exogenous infection of patients.

The topicality of the article is obvious since meningitis ranks third after lower respiratory tract infections and urinary tract infections in the structure of NIs at neurosurgical departments. The development of NM contributes to a longer stay in the CCU, and significantly lengthens the duration of inpatient treatment.

In this paper, the authors performed prospective observation using a large database including 1,153 patients. It is noteworthy that the diagnostics of nosocomial infectious complications of the central nervous system was based on the up-to-date approaches, and the cases were determined according to the Definitions of Nosocomial Infections.

The work by N.V. Kurdyumova, G.V. Danilov, O.N. Ershova, I.A. Savin, E.Yu. Sokolova, I.A. Aleksandrova, and M.A. Shifrin “Features of Nosocomial Meningitis in Patients of a Neurosurgical Critical Care Unit” was performed at a high scientific level and contains conclusions of practical interest. The references quoted in the article reflect the present-day point of view on the issue under investigation.

**Commentary**

V.V. Kulabukhov (Moscow, Russia)
Correlating a fMRI-Identified Activation Pattern of Language Areas with the Tumor Localization and Functional Asymmetry Profile in Patients with Intracerebral Tumors


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The aim of the study was to determine the dependence of activation patterns of language areas identified by functional magnetic resonance imaging (fMRI) on the functional asymmetry profile and tumor localization. Material and methods. Fifty patients were examined before surgical resection of intracerebral tumors of the temporal and frontal lobes. 33 patients had left-sided tumors, and 17 patients had right-sided tumors. The functional asymmetry profile was determined by self-assessment, the Annet questionnaire, and the dichotic listening task: 12 people were left-handers or retrained left-handers, and the remaining 38 patients were right-handers. fMRI was performed on a SignaHDxt magnetic resonance imaging machine (GE, USA) with a magnetic field strength of 3.0 T. The standard language block design paradigm was used in the study. The following tests were used: 1) reciting the months in reverse order; 2) naming nouns according to initial letters shown on the screen (K, L, M, N, R, S); 3) naming action pictures; 4) producing sentences using nouns shown on the screen; 5) listening to a text with headphones. The data were processed using standard BrainWavePA software (GE, USA). The Z-test in the range of 6 to 9 was used (p<0.001 was in all tests). Statistical data analysis included the nonparametric Spearman’s test for determining a correlation between lateralization of an identified activation area under speech load and the tumor localization (tumor is adjacent to the language area, invades it, or is distal of it) as well as between the functional brain asymmetry (left-handedness or right-handedness). Results. Activation of language areas on the left side only was identified in 16 patients (14 right-handers and 2 left-handers); in one left-handed patient, Broca’a area was detected only on the right side. In the other patients (like in right-handers with right-sided tumors), lateralization of language areas was different, in particular bilateral. Statistical analysis of the data demonstrated that bilateral activation of both Broca’a and Wernicke’s areas was more often observed in left-handers. Broca’a area was more frequently identified on the left, in the presence of a tumor distant from the area. This pattern did not apply to Wernicke’s area. Conclusions. The localization of Broca’a area activation is more dependent on the tumor location, while that of Wernicke area activation depends on the patient’s individual characteristics.

Keywords: preoperative fMRI, functional brain asymmetry, intracerebral tumors.

Currently, the indications for surgical removal of brain tumors, even from the region of language and motor areas, are expanded. The main objective of these surgeries is complete tumor resection, with the functionality of structures in the immediate vicinity of the tumor or involved in it being preserved as much as possible. For this purpose, intraoperative awakening of the patient for electrostimulated identification of motor and language areas is increasingly used in neurosurgery. During intraoperative electrostimulation, the language area localization was shown to have wide individual differences. For example, the speech system can be represented, partly or completely, in the contralateral hemisphere and have many additional language areas [1—4]. Therefore, preoperative preparation of the patient with an intracerebral tumor should include non-invasive examination of not only the lateralization but also the localization of language areas with respect to the tumor.

Today, functional magnetic resonance imaging (fMRI) is a leading non-invasive method to determine the localization of language areas that enables their identification and dynamic monitoring of the functional speech system state both after neurosurgical operations and after conservative treatment. However, according to some authors [5—7], the result of fMRI-based identification of the dominant hemisphere for speech may depend on the proximity of the pathological focus to putative language areas, used tests, and also features of statistical data processing.

Currently, fMRI is actively developed. It is noteworthy that studies have used a very diverse set of tests for selective activation of language areas, which is determined by aims and objectives of researchers. The most often used test to localize language areas is generation of verbs or naming nouns associated with pictures and initial letters [6, 8—14] as well as different variants of listening to syllables, texts, and sentences [15—17]. Less often, tests for speech activation include semantic and syntactic tasks (e.g., allocation of visually or verbally presented animals to different groups, identification of misspelled words and sentences, completion of sentences) whose solution actively involves Broca’s area [6, 7, 18, 19].

Most authors recommend using of several tests simultaneously to identify activation of language areas. In this case, it is noted that different tests may identify different language lateralization in the same patient [5,
Our previous fMRI study of 21 patients [20] also demonstrated the incidence rate of bilateral activity foci in speech tests. It was noted that the maximum difficulties arose in examination of patients with large malignant tumors with pronounced peritumoral edema when language areas were activated only on the right side in the presence of a left-hemispheric tumor and speech disorders.

The fMRI-based activation pattern of language areas (their lateral or bilateral representation) is crucial for neurosurgical practice. In this connection, a question arose of what may primarily determine the activation pattern: the functional asymmetry profile (right-handedness/left-handedness according to various parameters) or the tumor proximity to putative language areas. Whether the fMRI-based pattern of the individual functional speech system of a particular patient reflects bilateral activation areas under speech load, or it is a result of reorganization of this system due to tumor growth (brain plasticity)?

The study aim was to determine the dependence of activation patterns of language areas identified by fMRI on the functional asymmetry profile and tumor localization. The study objectives were as follows:

1) development and evaluation of a necessary and sufficient test battery to localize language areas in patients with focal brain lesions;
2) determination of the dependence of the activation pattern of language areas in patients with tumors of the temporal and frontal lobes:
   — on the functional asymmetry profile (right-handedness/left-handedness according to various parameters);
   — on the proximity of the areas to the tumor (comparison of patients with a tumor adjacent or spreading to the language area and those with a tumor not adjacent to the language area).

**Material and Methods**

Fifty patients were examined prior to intracranial tumor resection: 27 (54%) males and 23 (46%) females aged 14 to 70 years; the mean age was 34.5 years; the vast majority of patients were aged 14 to 50 years. The maximum age was 70 years; the minimum age was 14 years. The sex ratio was 1:1.4. The examined patients had no focal neurological losses. 7 patients had speech disorders in accordance with the tumor localization, with predominantly mild severity (in the case of temporal lobe tumor — acoustic-mnemonic aphasia; in the case of frontal lobe tumor — efferent motor aphasia); 3 of them were detected with mild hemiparesis or hemihypersphy.

The functional asymmetry profile was evaluated by self-assessment, the Annet questionnaire, and the dichotic listening task. According to the self-assessment and questionnaire, 12 people among the tested patients were left-handers or retrained left-handers performing most everyday actions (except eating and writing) with the left hand; the other 38 patients were right-handers (some had single signs of the left-handedness, according to the questionnaire). Dichotic listening was conducted in 33 patients (it failed in some patients due to speech disorders or gross auditory-verbal memory disorders). 23 patients had positive values of the right ear coefficient (REC), typical of left hemisphere speech dominance in right-handers. Negative and zero REC values indicating right hemisphere speech dominance or incomplete left hemisphere speech dominance were detected in 10 patients, with 3 of them being left-handers or retrained left-handers. It is worth noting a group of 7 patients with negative REC who considered themselves right-handers. Of them, 5 had large glioma with peritumoral edema in the left hemisphere; 2 had left-handers among relatives. A change in REC toward negative values (typical of left-handers) was detected in right-handers in the case of a large tumor in the left hemisphere, which may indicate speech system reorganization detectable during the dichotic listening test. However, this issue requires further investigation.

To qualify disorders of higher mental functions, all patients prior to fMRI underwent a full neuropsychological examination according to the Luria’s method [21] to exclude those who had contraindications for fMRI because fMRI requires the patient to be active, adequate, and capable of well understanding and keeping a task program and timely switching in accordance with the instructions.

We used a SignaHDxt magnetic resonance imaging machine (GE, USA) with a magnetic field strength of 3.0 T and a NordicNeuroLabActiva special station (GE, USA). In addition to standard pulse sequences in the T1 and T2 mode, the study included mandatory imaging in the 3DT1 FSPGR mode (for 4 min) with the 1 mm resolution in all coordinates and over the whole head. Automatic synchronization of sequence start was performed. fMRI examination with the use of a single test lasted 5 min 12 s.

The patients were asked to perform special task paradigms to activate different areas of the cerebral cortex during fMRI. A standard speech block design paradigm included:

1) 12-second preparation period required to determine the mean brain excitation level;
2) 5 rest periods (R) alternating with 5 activation periods (A), with the 30 s duration of each.

In the rest period, the patient did not perform any movements and lay motionless with eyes open; during
the activation period, the patient had to perform a task, which depended on the used paradigm. According to the literature data, the patient had to perform all tasks silently, without moving the tongue and the lips. These movements lead to activation of bilateral regions of the motor cortex in the precentral gyrus that are located near Broca’s area, which may complicate data processing. The patient just had to listen to the text, trying to understand its content. The patient was informed about the beginning of the activation period either by an audio signal through headphones or by commands displayed on the screen of special glasses.

To localize Broca’s and Wernicke’s speech areas, the following paradigms were selected (taken from literature, original and modified):

- reciting the months in reverse order;
- generation of nouns according to initial letters displayed on the screen (K, L, M, N, R, S);
- generation of verbs according to simple (not genre) pictures shown on the screen (e.g., house, horse, car, etc.; a total of 30);
- producing sentences according to nouns displayed on the screen;
- listening through headphones to a cognitive, emotionally indifferent text.

The first test was the original one and was suggested based on the ideas of classical aphasiology [21, 22] on the complexity of switching upon utterance of a de-automated series (counting and reciting the months in reverse order) in the case of affected Broca’s area. The remaining tests were prepared in principal accordance with the literature [6, 8—14], but were adapted to the study objectives and Russian language (e.g., nouns began with a consonant letter). The displayed pictures were simple and figural and did not cause difficulties in recognition.

The data were analyzed using BrainWavePA standard software (GE, USA) for processing of clinical data. Mapping of activation was accompanied by automatic segmentation of the anatomical data, motion correction of the functional data, smoothing with a 8-mm Gaussian spatial filter in all directions, and application of the basic linear multiple regression model using standard software. Assessment of the efficiency of freedom degrees of used programs was performed by the method of Worsley and Friston, which enables transformation of t-test maps into z-activation maps and matching of anatomical and functional AIR images by the method of Woods et al. We used the Z-test in the range of 6 to 9. There was $p<0.001$ in all tests.

Statistical data analysis included the nonparametric Spearman’s test for determining a correlation between lateralization of an identified activation area under speech load and the tumor localization (close to/distant from the language area) as well as between the right-handedness and the left-handedness.

### Results
Broca’s area was identified as an activation area in *pars triangularis* and/or *pars opercularis* in the posterior parts of the inferior frontal gyrus, sometimes on the border with the middle frontal gyrus. Wernicke’s area was identified as an area activated in response to speech loads strictly in the posterior part of the superior temporal gyrus or at the junction of the temporal and parietal lobes.

Presentation of a text to headphones (main test for identification of Wernicke’s area, according to the literature) led to that an extensive activation area of the primary auditory cortex was contiguous to Wernicke’s area (and merged with it), which made it difficult to identify the language area. For this reason, a special procedure was developed: statistical analysis of fMRI images was performed under the maximum Z-test value in the range of 8—9, which enabled a good differentiation between the primary auditory cortex and Wernicke’s area.

In addition to the standard language areas, speech loads also activated in all patients some other areas of the brain: the extra motor cortex was activated in almost all patients; various parts of the cerebellum were activated in most of the patients (in this case, activation areas in the hemispheres were contralateral to activation foci of Broca’s area); precentral areas of the brain in the projection of the oral musculature and some subcortical structures (thalamus, subcortical nuclei) were activated in several patients (in different tests). Analysis of the causes of activation of these brain parts requires further research. In addition, all patients were detected with activation of the visual cortex during visual presentation of letters or images and with activation of the auditory cortex upon listening to a text.

Assessment of the efficiency of various speech tests yielded the following data.

1. Broca’s area was activated in 31 (62%) of 50 patients upon reciting the months in reverse order: right-sided activation was observed in 5 (10%) patient; left-sided activation was in 18 (36%) patients; bilateral activation was in 8 (16%) patients. Activation of Wernicke’s area in this test was observed in 16 (32%) of 50 patients: activation was both in the left hemisphere and in the right hemisphere in 7 (14%) patients, and bilateral activation was in 2 (4%) patients.

2. Generation of nouns according to presented letters caused activation of Broca’s area in 39 (80%) of 49 patients: right-sided activation was in 6 (12%) patients;

### Table 1. Tumor localization in brain lobes in examined patients

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Lobe</th>
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<tbody>
<tr>
<td></td>
<td>temporal</td>
<td></td>
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<tr>
<td>Left (n=33)</td>
<td>16</td>
<td></td>
<td></td>
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<tr>
<td>Right (n=17)</td>
<td>7</td>
<td>10</td>
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</table>
left-sided activation was in 26 (53%) patients; bilateral activation was in 7 (14%) patients. Wernicke’s area was activated in 24 (49%) patients; left-sided activation was observed in 17 (35%) patients; right-sided activation was in 2 (4%) patients; bilateral activation was in 5 (10%) patients.

3. Generation of verbs according to presented pictures caused activation of Broca’s area in 35 (74%) of 47 patients: right-sided activation was in 4 (9%) patients; left-sided activation was in 23 (49%) patients; bilateral activation was in 8 (17%) patients. Wernicke’s area was activated in 15 (32%) patients: right-sided activation was in 2 (4%) patients; left-sided activation was in 10 cases (21%); bilateral activation was in 3 (6%) patients.

4. Producing sentences with suggested nouns activated Broca’s area in 40 (87%) of 46 patients: right-sided activation was observed in 6 (13%) patients; left-sided activation was in 27 (59%) patients; bilateral activation was in 7 (15%) patients. Wernicke’s area was activated in 30 (65%) patients: right-sided activation was in 2 (4%) patients; left-sided activation was in 23 (50%) patients; bilateral activation was in 5 (11%) patients.

5. Listening to a text is a specific test for mapping of Wernicke’s area. This area was activated in 35 (73%) of 48 patients: right-sided activation was observed in 4 (8%) patients; left-sided activation was in 16 (33%); bilateral activation was in 15 (31%) patients. Broca’s area is not activated by this test.

To determine the dependence of the localization of activation foci in response to speech tests on the functional asymmetry profile, the number of activation foci was counted in right-handed patients (38 patients) and left-handed patients (12). The data are presented in Table 2. The total number of activation foci in right-handed patients was 88: Broca’s area was activated 48 times, and Wernicke’s area was activated 40 times (bilateral activation was considered as 2 foci). The total number of activation foci in left-handed patients was 35: Broca’s area was activated 18 times, and Wernicke’s area was activated 16 times (bilateral activation was considered as 2 foci). According to fMRI, speech load caused activation of 2.32 foci in a right-handed patient and 2.92 foci in a left-handed patient, on average. The left-handers had a larger number of activation foci in the contralateral hemispheres, and this result was statistically significant (Spearman’s rank correlation coefficient: \( r = -0.322 \)). Thus, lateralization of activation foci depends on the functional asymmetry profile (right-handedness/left-handedness).

To evaluate the dependence of fMRI identification of activation foci of language areas on the tumor localization, a group of 20 patients with tumors of the frontal and temporal lobes of the left hemisphere was specifically selected. In these patients, the tumor was immediately adjacent to putative language areas or spread to them. The results of statistical data processing demonstrated that Broca’s area was statistically significantly more often activated in the left hemisphere in the presence of tumors distant from it (\( r = -0.302 \)). Different types of Broca’s area activation (left-sided and bilateral; in single cases with glioblastomas and pronounced edema — right-sided only) were identified in the presence of tumors adjacent to language areas or invading them. It is important that this pattern did not apply to Wernicke’s area. Its localization was correlated with the ear to which the patient brought the phone. Interestingly, the right-handers more often brought the phone to the right ear only, less often — to both ears, and even more rarely — to the left ear only. However, the left-handers never brought the phone to the right ear only; they brought the phone to the left ear only or to both ears (\( r = 0.504 \)). If the phone was brought to the right ear only, then Wernicke’s area was more frequently detected on the left side (\( r = 0.427 \)). This is due to the fact that speech perception is primarily involved in both a phone conversation and listening to a text.

**Discussion**

When five speech tests were used, activation areas were identified in all patients, but had a different localization. However, the situation was more complex in 2 patients with very large glioblastomas of the fronto-temporal and temporo-frontal localization; in one case, Broca’s area was not identified at all (but 2 Wernicke’s areas were activated in the contralateral hemispheres); in the other case, no language areas were activated in the left hemisphere (only an activation area homologous to Broca’s area in the right hemisphere was observed). Both of these patients at admission had acoustic-mnestic aphasia, with the second patient presenting with a more severe form of it and with elements of effferent motor aphasia. Glioblastomas in these patients were surrounded by large peritumoral edema and spread directly to language areas. The causes for the complexity of fMRI-based identification of language areas in patients with large malignant tumors were discussed previously [20].

Most of the examined patients (33 (66%) out of 50) were detected with a rather mixed activation pattern in response to speech stimulation. In most of the right-handed patients with a right-sided tumor, bilateral activation of language areas could be observed (Wernicke’s area was especially often involved); activation of one and another language area on both sides and bilateral activation of Broca’s or Wernicke’s area could be observed in various tests (Figs. 1—4).

Analysis of the data on activation of language areas revealed a large percentage of bilateral activations: only 16 (32%) of 50 patients had one left-sided activation of Broca’s area and Wernicke’s area; in the remaining patients, there was bilateral representation of at least one language area. Of these 16 patients, 9 were diagnosed with a tumor on the left side, and 7 were diagnosed with a tumor on the right side. Interestingly, 2 of 9 patients...
(with left-sided tumor) were retrained left-handers; the others of 16 patients were right-handers. These patients were congenital left-handers with left-sided tumors who had only one Broca’s and Wernicke’s activation area in the left hemisphere. Another left-handed patient (without family left-handedness) was detected with Broca’s area located predominantly on the right side (left-sided area was minimally activated); however, Wernicke’s area was activated distinctly on one side, but on the left. The patient was diagnosed with a tumor of the right frontal lobe that was adjacent to the language activation area detected by fMRI (Fig. 4). In the Wada test, speech disorders were detected in the case of right-sided drug administration. Electrostimulation of the language area of the right frontal lobe during surgery with awakening caused arrest of speech; after the operation, slight efferent motor aphasia was observed; i.e., in this patient, the right-sided localization of Broca’s area was fully verified, but Wernicke’s area was identified on the left (according to fMRI).

Of the used tests, the most effective test was producing sentences according to visually presented nouns: it allowed identification of Broca’s area in 87% of cases. Importantly, it also allowed identification of Wernicke’s area in 65% of patients (totally, in patients with different tumor lateralization). In this case, the percentage of Wernicke’s area activation in this test was only slightly lower than in listening to a text (73%). And this is not surprisingly: producing sentences is the most difficult speech task that requires joint work of various parts of the speech system: understanding the presented word and finding words semantically appropriate to it are functions of the temporal lobe; proper arrangement of words in a sentence and grammar are functions of Broca’s area. Two other tests were also effective: generation of nouns according to presented letters (activation of Broca’s area was in 80% of cases; activation of Wernicke’s area was in 49% of cases) and generation of verbs according to presented pictures (activation of Broca’s area was in 74% of cases, and activation of Wernicke’s area was in 32% of cases). It is necessary to pay attention to the frequency of Wernicke’s area activation upon carrying out these three tests by patients, although the literature discusses their use only for activation of Broca’s area [23, 24]. The test for generation of verbs, particularly recommended in the literature for activation of Broca’s area [9], turned out to have no advantages over other tests because actualization of verbs is disturbed in Broca’s aphasia; also, “telegraphic speech” may occur in Broca’s aphasia [21, 22].

This different activation of language areas in patients in response to the used tests primarily reflected individual features of the functional speech system of a particular patient and his previous experience. For example, the first test of reciting the months in reverse order, which caused Broca’s area activation only in 62% of patients, was probably not sufficient for speech load in most of the patients. Naming nouns according to pictures and producing sentences according to the presented word (the most difficult speech tasks) activated not only Broca’s areas in the maximum number of patients (up to 87%) but also Wernicke’s areas (up to 49%), i.e., performing these tasks involved various parts of the functional speech system, but very individually.

Often, bilateral identification of Wernicke’s area activation may also be associated with that perception of well known short words during listening to a text can occur in the right temporal lobe as well. This was previously shown in patients with a “split-brain” [25]. Apparently, the right temporal lobe of investigated patients was involved in perception of a speech material to a different degree. All this may indicate that lateralization of Wernicke’s area is associated with the

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Footnote. * during counting, bilateral activation was considered as 2 activation foci.
individual organization of the speech system to a greater degree than lateralization of Broca’s area.

Currently, there are many studies related to investigation of reorganization of the functional speech system in stroke patients [8, 26—28], in surgical treatment of patients with pharmacoresistant epilepsy [23, 29] as well as in patients with brain tumors [30, 31]. For example, A. Thiel et al. [31] in 2001 reported plasticity of the speech system in patients with tumors (based on the PET data). S. Partovi et al. [24] in 2012 identified a change in the localization of activation areas in patients after tumor resection. Investigation of recovery of not only speech but also movements demonstrated that in the presence of paresis after tumor resection, bilateral activation areas arise in the brain in response to movement of the paretic arm [32, 33]. However, analysis of studies investigating the functional speech system in the presence of focal lesions revealed that patients with a left-sided lesion, right-handers or left-handers, were mainly examined, while patients with the right-sided localization of a lesion were examined only if they were left-handers, and the right-sided localization of language areas was assumed. Activation of language areas in right-handed patients with right-sided lesions was virtually unexplored. However, its study would complete the picture of individual differences in the structure of the functional speech system in the presence of a lesion, and the study should be continued.

Therefore, this study demonstrated that the pattern of identified activation foci of language areas (on the basis of fMRI) depends on both the individual organization of the functional speech system (primarily, Wernicke’s area) and the presence of a tumor near language areas (in particular, Broca’s area).
Conclusions
1. The proposed tests to activate language areas during fMRI proved to be adequate for examination of patients with gliomas.
2. The most effective tests to activate language areas during fMRI were as follows: naming nouns according to presented letters, naming action pictures, and producing sentences according to presented nouns as well as listening to a text. However, these tests should be used in combination since activation of language areas in response to the suggested tests might be identified differently, which does not exclude misinterpreting lateralization of language areas.
3. Lateralization of language area activation depended on both the individual organization of the functional speech system and the tumor localization (whether the tumor is immediately adjacent to the language area or invades it, or not).

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As well as the effect of tumor localization on activation of the asymmetry of language areas in right-handers and left-handers. Verification of secondary motor and sensory language areas, the authors suggested the use of several paradigms for accurate localization and with different functional asymmetry profiles. With intracerebral tumors of mainly frontal and temporal algorithms of fMRI for mapping of language areas in patients usual topography. It should be noted that activation (increased cerebral blood flow) of areas in both hemispheres during fMRI is not always related to functional manifestations. For example, fMRI examination of healthy volunteers (right-handers) often reveals activation of language areas in both hemispheres; however, patients (right-handers) who underwent right-sided ischemic stroke rarely develop aphasia in contrast to patients with left hemispheric strokes. Investigation of the role of right hemispheric homologues of language areas as well as tertiary hemispheric strokes. Investigation of the role of right hemispheric homologues of language areas as well as tertiary hemispheric strokes.


Commentary

Over the past decades, non-invasive mapping of the eloquent brain areas, such as motor and language areas, has become increasingly popular in preoperative brain mapping due to introduction of neuroimaging techniques into clinical practice. The complexity of studying the language cortex is associated with its predominant lateralization and its certain variability in different people. In addition, tumor growth results in a displacement of functionally important regions from their usual topography.

This article highlights the problem of choosing the optimal algorithms of fMRI for mapping of language areas in patients with intracerebral tumors of mainly frontal and temporal localization and with different functional asymmetry profiles. The authors suggested the use of several paradigms for accurate verification of secondary motor and sensory language areas, demonstrated an individual variability of the functional asymmetry of language areas in right-handers and left-handers as well as the effect of tumor localization on activation of the language cortex, analyzed in detail the results of examination of a sufficiently large number of patients, and suggested algorithms of preoperative clinical fMRI examination of the patient for precise mapping of language areas. The use of fMRI with speech loads is very important for identification of the language area localization with respect to the tumor and also for examination of these patients over time.

It should be noted that activation (increased cerebral blood flow) of areas in both hemispheres during fMRI is not always related to functional manifestations. For example, fMRI examination of healthy volunteers (right-handers) often reveals activation of language areas in both hemispheres; however, patients (right-handers) who underwent right-sided ischemic stroke rarely develop aphasia in contrast to patients with left hemispheric strokes. Investigation of the role of right hemispheric homologues of language areas as well as tertiary language areas requires further research.

M.V. Krotenkova (Moscow, Russia)
Growing Teratoma Syndrome in a Patient with Intracranial Germ Cell Tumor

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A six-year-old patient with non-germinomatous germ cell tumor of the chiasmatic-sellar area developed polyuria and polydipsia as the first symptoms of the disease. Then there were signs of precocious puberty and vision impairment. MRI examination revealed a chiasmatic sellar tumor and occlusive hydrocephalus. Tumor marker levels in blood serum were elevated. The alphafetoprotein level was increased 5-fold; human chorionic gonadotropin 20-fold. These levels increased over time. The patient received 2 cycles of PEI multiagent chemotherapy (Ifosfamide 1.5 g/m2, Cisplatin 20 mg/m2, and Etoposide 100 mg/m2) during 5 days and 1 cycle of second-line multiagent chemotherapy (Cisplatin 100 mg/m2 for 1 day and Endoxan 1500 mg/m2 for 2 days). Despite the decrease in tumor marker levels to normal values, the patient’s vision still deteriorated. MRI examination revealed that tumor size increased and its structure changed. Total tumor resection led to vision improvement and regression of intracranial hypertension. Histological analysis of tumor tissue only revealed a mature teratoma. This phenomenon, known as growing teratoma syndrome, is very rare among patients with intracranial non-germinomatous germ cell tumors.

**Keywords:** intracranial germ cell tumor, multiagent chemotherapy, growing teratoma syndrome.

Primary intracranial germ cell tumors (GCTs) are rare types of tumors and are usually found in children and adolescents than in adult patients, accounting for 0.5—1% in the East and 2—5% in Japan [1—3]. The incidence rate of teratomas, including malignant forms, is 0.4% of all brain tumors [4]. Intracranial GCTs most frequently localize in the pineal and chiasmatic-sellar areas (neurohypophysis) [2, 3]. GCTs are divided into germinomas and non-germinomatous germ cell tumors (NGGCTs). The non-germinomatous germ cell tumors include mature and immature teratoma, teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor, and choriocarcinoma.

Diagnosis of GCTs includes contrasted and uncontrasted magnetic resonance imaging (MRI) and measurement of tumor markers: alpha-fetoprotein (alpha-FP) and human chorionic gonadotropin (hCG) levels in blood and cerebrospinal fluid. Multagent chemotherapy incorporating Cisplatin is most efficient in treatment of malignant intracranial GCTs. Combination therapies with Cisplatin and Etoposide have yielded favorable immediate results (80%) [5, 6].

The growing teratoma syndrome was first described by C. Logothetis et al. [7] in 1982 for extracranial GCTs. The literature mostly describes retroperitoneal GCTs and intracranial NGGCTs only in a few cases [7—10]. Intracranial growing teratoma syndrome (IGTS) is known to be a rare condition; its frequency is about 6.5% of all intracranial GCTs [9, 10]. The diagnosis of the growing teratoma syndrome is based on three criteria: the normalization of initially high alpha-FP and/or hCG levels, increasing the size of the tumor during or after chemotherapy, and histologically confirmed mature teratoma in patients with NGGCTs [5—7].

The growing teratoma syndrome is reported to develop mostly in patients with mixed GCTs and immature teratoma [8—10]. Based on increasing the tumor’s size at multiagent chemotherapy physicians primarily suspect continued tumor growth.

We present a case of treatment of 6-year-old boy with intracranial growing teratoma syndrome in the chiasmatic-sellar area (CSA).

**Clinical case**

A 6-year-old boy presented with polydipsia and polyuria. Diabetes insipidus was diagnosed. MRI revealed thickened pituitary stalk. A year later there were signs of precocious puberty (penis growth, the emergence of the sexual body hair, changes in voice, and gynecomastia), vision impairment, and vomiting.

In the ophthalmic examination on both eyes (OU), visual acidity was significantly deteriorated (Vis OD=0.3, OS — 0.1) and temporal hemianopia was detected. Neurological examination revealed symptoms of intracranial hypertension (vomiting, optic disk edema on fundus). Partial hypopituitarism (growth hormone deficiency, hypothyroidism, hypocorticism) was found at endocrinological examination in addition to precocious puberty and diabetes insipidus. Alpha-FP level in blood serum was elevated to 26.67 ng/ml (normal limits are up to 4.6 ng/ml), hCG level was elevated to 200.1 IU/ml (normal values are up to 9 IU/ml). Results of other
biochemical parameters were within normal limits. From this period, the patient has received hydrocortisone (5—10 mg/day), desmopressin (0.05—0.1 mg per day depending on diuresis), and L-thyroxine (50 µg/day) continuously as replacement therapy.

MRI revealed a tumor in the CSA, which spread to the third ventricle and left foramen of Monro. Signs of occlusive hydrocephalus were found (Fig. 1). Clinical and radiological presentation was indicative of GCTs. Spinal cord examination excluded tumor metastasis. Tumor cells in CSF from the lumbar region were not examined. The Mx staging was defined. Repeated examination of tumor markers in the blood before multiagent chemotherapy showed elevated alpha-FP levels 2-fold of the initial level (up to 55.86 ng/ml) and hCG level up to 405.34 IU/ml.

The patient received 2 cycles of PEI multiagent chemotherapy with an interval of 3 weeks as in SIOP GCT-96 protocol: Cisplatin 20 mg/m² (5 days), Etoposide 100 mg/m² (3 days), and Ifosfamide 1500 mg/m² (5 days). Tumor markers in serum were normalized after the second cycle of multiagent chemotherapy and were as follows: alpha-FP — 6.13 ng/ml and hCG — 0 IU/ml. Meanwhile, MRI after 2 cycles of multiagent chemotherapy showed an increase in the chiasmatic sellar tumor’s size, cystic component dominated in the structure of the tumor. Brain metastases were absent (Fig. 2).

In addition, the patient received 1 cycle of second-line multiagent chemotherapy: Cisplatin 100 mg/m² (1st day) + Endoxan 1500 mg/m² (1st and 2nd days). Repeated MRI after 2 weeks after multiagent chemotherapy revealed that the tumor continued growth in the CSA and the number of cysts in the tumor increased (Fig. 3). Alpha-FP and hCG levels remained stable within the normal limits: 3.4 ng/ml and 0 IU/ml, respectively.

Visual acidity still deteriorated as shown by OU ophthalmic examination: Vis OD=0.1—0.15, OS — light perception.

Because of the increased sizes of the tumor despite chemotherapy causing progressive vision impairment, the patient was subjected to total resection of the chiasmatic sellar tumor at the Burdenko Neurosurgical Institute. During surgery, a tumor of a very thick consistency, which composed of light gray colored connective tissue and contained a large number of cysts of different sizes, was resected.

The results of histological and immunohistochemical studies revealed mature teratoma; immature and malignant elements were absent. Immunohistochemical study revealed that the tumor tissue was negative for alpha-FP and hCG (Fig. 4).

In the first days after surgery all types of voluntary activity sharply decreased, paroxysmal extrapyramidal symptoms developed in the form of stereotyped movements in hands and hand tremor and disturbance of thermoregulation with febrile hyperthermia. Based on electroencephalography, epileptiform activity was not detected. Spontaneous activity began to grow starting from the 3—5th day: the patient began to sit in bed, walk with support, and communicate with others. Moderate motor deficit in the right extremities gradually grew over time. The symptoms of intracranial hypertension regressed completely after surgery.

Left outer subdural drain was placed because of hyperthermia, growth of right-sided hemiparesis and subdural fluid accumulation (more on the left). The therapy improved the patient’s condition, level of activity increased, range of motion in the right extremities and the volume of speech began to rise. After 5 days, the outer subdural drain was removed.

Contrasted and uncontrasted brain MRI after the operation showed the absence of the tumor remnants in the CSA and the third ventricle, metastases in brain structures were not detected (Fig. 5). Tumor cells in the cerebrospinal fluid on the 14th day after the surgery were not identified. Alpha-FP and hCG levels in serum were negative. Neuroophthalmologist reported visual improvement to 0.5 on the right and to 0.2 on the left eye.

The patient received radiation therapy on the brain as a prophylactic measure after 4 weeks after surgery in the total focal dose of 30 Gy. The patient was on the follow-up for 37 months over-time. Currently, the boy is doing well, attends secondary school, attends extra classes of English, and goes swimming. Visual impairment still remains at 0.7 on the right and 0.04 on left. Right-sided homonymous hemianopsia and other neurological disorders are absent. Deficiency of pituitary hormones is compensated for by intake of L-thyroxine (75 µg/day), hydrocortisone (2.5—10 mg/day), and desmopressin (0.05—0.1 mg/day).

MRI over time shows a lack of the tumor and metastasis, alpha-FP and hCG levels remain negative so the patient has a risk of the tumor relapses (Fig. 6).

Discussion

Teratomas constitute about 0.5% of all intracranial tumors. Ten-year survival of patients with mature and immature teratomas is 90 and 70%, respectively. Patients with malignant transformation of teratoma show worse survival of less than 50% [4, 6].

Reduction of alpha-FP and hCG tumor marker levels in the blood, a paradoxical increase in the size of the tumor at multiagent chemotherapy, and verified histological diagnosis of mature teratoma after resection of the tumor indicate the growing teratoma syndrome. Intracranial growing teratoma syndrome is very rare, the literature describes single cases.

The growing teratoma syndrome in our patient manifested after the second cycle of chemotherapy. The period from the detection of the tumor before the
The diagnosis of growing teratoma syndrome took 3.6 months.

The etiology of the growing teratoma syndrome remains unknown. Chemotherapy plays a potentially important role in the etiology of this syndrome. The most quoted causes of this syndrome include three aspects:

1. Chemotherapy destroys only the cancer cells leaving mature benign elements.
2. Chemotherapy causes a change in the kinetics of cells and transformation of a malignant tumor into a benign mature teratoma.
3. The third hypothesis (W. Hong et al. [11]) suggests that malignant cells differentiate into benign under the influence of chemotherapy [9, 11].

Growing teratoma represents a mixed secreting GCT, which is sensitive to chemotherapy, and a nonsecreting mature teratoma, which continues to grow during chemotherapy.

Several factors may be predictive of the growing teratoma syndrome; these include increasing the size of
Continued growth of the chiasmatic-sellar tumor, the number of cysts in the tumor increased.

The therapy for intracranial growing teratoma should include surgery. Radiotherapy is not required after total resection of the tumor and when metastases are absent [8—10]. The presence of tumor remnants and/or metastases after partial resection has a poor prognosis, since a growing tumor, which is represented by a mature teratoma on histologic presentation, is insensitive to either radiation therapy or chemotherapy [9]. Early detection of the phenomenon of the growing teratoma syndrome and early resection of the tumor are crucial to cure the patient.

The good results of the therapy of growing teratoma syndrome rely on four factors: 1) knowledge of this phenomenon; 2) thorough diagnostic examination of patients with GCTs when the patient is subjected to chemotherapy; 3) early detection of the paradoxical response of the tumor to chemotherapy (increasing the size of the tumor and the normalization of tumor markers in the blood); 4) total resection of the tumor.

C. Kim et al. in his publication [9] showed that among nine patients with total resection of the growing teratoma only one patient relapsed with GCTs, the remaining eight patients are alive without recurrence (continued tumor growth).
Thus, the prognosis of intracranial growing teratoma depends on the scope of surgical intervention.

Conclusions

Early identification of the growing intracranial teratoma during or after chemotherapy of non-germinomatous GCTs is based on the analysis of tomograms over time. Typical signs of intracranial growing teratoma are multicystic transformation and increasing the size of the tumor based on MRI data, and the normalization of tumor markers during chemotherapy. The curative method for the patient is total surgical resection of the tumor.

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Research studies in neurooncology are relevant since they allow validation of efficient programs to cure CNS tumors. Analysis of the case, which is rare in the practice, is of interest to the practitioner, as it shows the most effective treatment of the disease.

It is known that the prognosis of patients with germ cell tumors varies and depends primarily on the histological presentation of tumors, as well as on the response to chemoradiotherapy. Increased tumor size at multiagent chemotherapy primarily assumes continued tumor growth. Early detection of growing teratoma syndrome and early resection of the tumor are crucial to cure the patient.

The paper presents a rare case of intracranial growing teratoma in the chiasmatic-sellar area in a 6-year old child. A thorough diagnostic examination of the patient with GCTs during chemotherapy showed continued tumor growth and multicystic transformation while the alpha-FP level normalized. Total surgical resection of the tumor was found to be the curative method for the sick child.

The article presents the literature data showing that good results of growing teratoma syndrome treatment depend on the following factors: 1. Knowledge of this phenomenon. 2. Thorough examination during chemotherapy. 3. Early detection of the paradoxical response to chemotherapy (increasing the size of the tumor and the normalization of tumor markers in the blood). 4. The total resection of the tumor.

The article is of great interest to readers of this journal.

V.E. Popov (Moscow, Russia)
Cardiac Arrest after Induction of Anesthesia in Neurosurgical Patients (Analysis of Two Clinical Cases)

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The paper reports two clinical cases observed in the Burdenko Neurosurgical Institute with a time lag of four years. Both patients showed severe clinical symptoms of intracranial hypertension before surgery. Immediate full-scale resuscitation was required in both cases due to asystole that developed immediately after induction of anesthesia and tracheal intubation. 

Objective. The objective of the study was to analyze the possible causes of the complication and preventive measures. 

Material and Methods. The first patient (33 years of age) diagnosed with multiple space-occupying brain lesions underwent resuscitation for cardiac arrest after induction of anesthesia, but emergency measures were not effective and the patient was certified dead. The second patient (28 years of age) diagnosed with cystic cerebellar tumor also experienced cardiac arrest after induction of anesthesia. During resuscitation, the anterior horn of the right lateral ventricle was punctured and then cardiac activity was successfully recovered. 

Results. In both patients, tonsillar herniation into the foramen magnum after induction of anesthesia was detected based on the clinical presentation, postmortem diagnosis, and successful drainage of the cerebrospinal fluid. Possible causes of complications and preventive measures were discussed. Conclusion. Under certain circumstances, neurosurgical patients with intact cardiovascular system can face a risk of cardiac arrest at any stage of surgery. In neurosurgical patients, a cystic mass compressing the floor of the fourth ventricle and hypertensive crisis before surgery are the risk factors for tonsillar herniation into the foramen magnum after induction of anesthesia, followed by cardiac arrest.

Keywords: intracranial hypertension, anesthesia, cardiac arrest.

Cardiac arrest in patients at any stage of anesthesia is always difficult and disastrous for both the patient and anesthesiologist. The problem is complex and multidimensional, so let us specify right away that it comes not for patients with severe cardiovascular pathology (in the case of cardiovascular pathology, the risk of this complication is quite evident), but for those with the intact cardiovascular system. Neurosurgical patients with intracranial pathology are at the risk of this severe complication under certain circumstances. The description of two similar clinical cases observed in our practice at two-year intervals is presented below and analyzed with allowance for literature data.

Description of clinical cases

Case report 1

A 33-year-old male patient K., a truck driver with body weight of 57 kg, was admitted to the Burdenko Neurosurgical Institute with a diagnosis of “multiple space-occupying brain lesions” in November, 2007. His past medical history revealed that the first signs of the disease appeared in August, 2007 as coordination impairments followed later by headaches. Impairment of health occurred after 2 months when the intensity and incidence of headaches sharply increased. Examination of the patient at the Burdenko Neurosurgical Institute revealed balance and gait impairments and incoordination in the limbs on the background of pronounced intracranial hypertension characterized by morning headaches, nausea, vomiting, and retinal venous congestion. CT and MRI of the brain and cervical spine revealed multiple intracranial cystic neoplasms: a large node in the fourth ventricle projection and three nodes in the left occipital region (Fig. 1). Interestingly, no typical hydrocephalus (enlargement of the ventricles) was observed. Physical status of the patient revealed no significant anomalies with the exception of resting ECG signs of inadequate coronary blood supply into the high lateral regions of the left ventricle (Fig. 2), in the absence of any clinical symptoms.

On the basis of clinical presentation and MRI data, which showed a multifocal and multiple lesion, the presence of a pronounced cystic component, and the absence of perifocal edema, parasitic brain infection (cerebral echinococcosis) was suspected. For this reason, the patient consulted the specialists of the Department of Medical Parasitology and Tropical Medicine at the Clinical Center of the I.M. Sechenov First MGMU. According to their recommendations, the patient underwent ultrasound of the abdominal and pleural cavities and urogenital ultrasound; however, neither any abnormalities were detected, nor were specific antibodies in his blood. Given the severe syndrome of intracranial hypertension and the lack of signs of damages to internal organs, the treatment strategy was as follows: intracranial neurosurgical procedure with single-stage resection of the abnormal nodes in the

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occipital lobe and lumen of the fourth ventricle, followed by antiparasitic chemotherapy in the postoperative period. The day before surgery, the patient felt a sudden headache followed by nausea and vomiting and his upward glance was restricted, which was regarded as occlusive hydrocephalus. The latter was stopped using the conventional method, and the doctors on duty were recommended to apply the external ventricular drainage in the case of recurrent attack.

On the morning of the surgery, the patient was transferred to the operating room without any premedication. In the operating room, the catheter was inserted into his peripheral vein, through which he received initial crystalloid infusion. During standard monitoring (3-lead electrocardiogram (ECG), noninvasive blood pressure monitoring, capnography, and pulse oximetry) the patient intravenously received: Dormicum (5 mg), propofol (200 mg), fentanyl (0.2 mg), rocuronium bromide (4 mg), and Lysthenon (200 mg). As these drugs began to work, supportive mechanical ventilation with 100% oxygen using an oxygen mask of the anesthetic machine was initiated. Tracheal intubation was successful at the first try and caused no complications. Mechanical ventilation was provided through the endotracheal tube as the intermittent positive-pressure ventilation. After 3 minutes, however, persistent bradycardia was detected (heart rate was as low as 30 bpm) and the blood pressure (BP) rapidly fall to

![Fig. 1. T2-weighted MRI of the male patient K., sagittal (a and b) and axial (c) views, 19 days before surgery.](image)

Three cystic nodes in the left occipital region (a) and in the cavity of the fourth ventricle (b) with the absence of perifocal brain edema are visualized. Insignificant tonsillar herniation below the foramen magnum level, the absence of hydrocephalus, and displacement of medial brain structures are noteworthy.

![Fig. 2. Preoperative ECG of the patient K.](image)

Signs of slightly reduced coronary blood flow into the superolateral left ventricle.
70/30 mmHg. Subsequently, asystole was visualized on the monitor; BP was not detectable. In this regard, full-scale resuscitation was initiated immediately (closed-chest massage, catheterization of the right subclavian vein, bolus infusion of 6% hydroxyethyl starch solution and soda, intravenous administration of sympathomimetic drugs and corticosteroids, and repeated defibrillation). However, the aforementioned resuscitation failed and the patient was certified death after 40 minutes.

Postmortem examination confirmed the clinical diagnosis of the parasitic brain infection (Figs. 3, 4). Disseminated parasitic infection to the internal organs, which was not diagnosed preoperatively by ultrasound, was detected (multiple cysts in the liver, kidneys, and even in the myocardium) (Figs. 5—7). This finding, as well as a scar in the posterior part of the apical region of the interventricular septum could explain the ECG changes in a young person with no coronary artery disease. Three cysts with transparent colorless liquid content were observed in the occipital lobe of the left cerebral hemisphere. A similar cyst was observed in the lumen of the fourth ventricle. Brain tissue was edematous, with signs of cerebellar tonsillar herniation into the foramen magnum, which was the cause of death.

**Case report 2**

A 28-year-old male patient O., a dentist with body weight of 62 kg, was admitted to the Burdenko Neurosurgical Institute with a diagnosis of “cystic tumor of the cerebellum, occlusive hydrocephalus”. After a viral infection three months before admission, the patient complained of periodic headaches, nausea, and vomiting, as well as of dizziness, gait impairment, and coordination impairment in both hands. A significant worsening of the neurological symptoms in the form of headache aggravation occurred one week before the admission to the Burdenko Neurosurgical Institute. MRI of the brain revealed a cerebellar mass with a cystic component and occlusive hydrocephalus (Fig. 8).

The patient was presented with relatively satisfactory condition during examination at the Burdenko Neurosurgical Institute. On the background of the intracranial hypertension syndrome presented by paroxysmal hemicrania with nausea and vomiting during the acute phase, the clinical presentation of the disease included symptoms of the posterior cranial fossa (PCF) lesions causing multiple spontaneous horizontal nystagmus, balance and gait impairments, and incoordination of the upper and lower limbs. Ophthalmoscopy revealed no signs of intracranial hypertension.

No anomalies were observed in the physical status of the patient, including the state of the cardiovascular system. Previously, the patient had undergone only one surgical intervention (rhinoplasty). On the basis of the ECG results, no anomalies were observed except the insignificant intraventricular conduction delay (Fig. 9).

The day before surgery, the symptoms of acute occlusive hydrocephalus were developed, so the possibility of applying the external ventricular drainage was discussed, but the crisis was stopped by drug administration. The patient was leaved under supervision of the doctors on duty with instructions to use the ventricular drainage immediately in the case of a recurrent attack.

The next morning, the patient was transferred to the operating room without any preanesthetic medication. After the peripheral venous catheter was inserted, intravenous crystalloid infusion was initiated. The
closed-chest massage, mechanical ventilation with 100% oxygen, intravenous crystalloid infusion, and then HyperHAES (250 mL), soda, as well as intravenous atropine, epinephrine, and dexamethasone. Single defibrillation allowed to restore the own heart rate of the patient. During resuscitation, neurosurgeons punctuated the anterior horn of the right lateral ventricle during 2—3 minutes. The thus obtained transparent colorless cerebrospinal fluid outflowed under high pressure (as a liquid jet), so external ventricular drain system was adjusted. Within 30 minutes, the doctors managed to fully stabilize the cerebral hemodynamics and made a coordinated decision to move forward with surgery.

With the patient lying in the prone position, the occipital squama over the medial regions in both hemispheres and the part of the arch of the atlas were resected via midline suboccipital approach. Hemangioblastoma (angioreticuloma) of the cerebellar hemisphere was resected. The duration of the surgery was 4.5 hours; blood loss was less than 500 mL.

The postoperative period was complicated, but no major problems occurred. During the patient’s stay in the intensive care unit (5 days), he fully recovered consciousness on the background of stable vital functions, and then he was transferred to his ward. However, during feeding after 2 days, the aspiration of food occurred and the patient was transferred again to the intensive care unit and underwent percutaneous dilatational tracheostomy for the purpose to protect the respiratory tracts from aspiration on the background of pronounced pseudobulbar disorders. After 3 days, the patient was transferred again to his ward. Further healing proceeded normally. The patient was discharged on the 15th...
postoperative day. At that time, the neurological symptoms regressed, endotracheal tube was removed, and mental and emotional well-being of the patient was stabilized.

Discussion

Two aforementioned clinical cases significantly differ from each other in the main clinical diagnosis and outcome. But still they also have certain similarities, which allows making the following conclusions after analysis of these clinical cases:

1. Both patients were young males without any severe chronic cardiac pathology. However, before surgery, the first of them showed difficult to be explained ECG changes, and bullae of echinococcus in his heart and scars of unknown origin were revealed during his autopsy, but all of this could hardly be the cause of a sudden asystole unresponsive to resuscitation.

2. In both patients, acute intracranial process caused the development of the intracranial hypertension syndrome; the second patient also experienced severe occlusive hydrocephalus. In both cases, clinical symptoms of intracranial hypertension were the main manifestation of the disease and developed rapidly. This fact can possibly explain the absence of papilledema.

3. In both patients, clinical symptoms indicated extremely severe intracranial hypertension. Moreover, on the background of clear consciousness on the day before surgery, both patients showed clinical symptoms
of occlusive hydrocephalus in the form of an episode of severe headache, nausea, vomiting, and upward glance limitation. For both patients, teams of doctors on duty discussed the necessity of the external ventricular drainage, but they still refused to use it due to the effects of dehydration therapy and the lack of vital impairments after the procedure.

A fundamental question arises: what happened to our patients at the stage of induction of anesthesia and tracheal intubation, which caused sudden asystole on the background of initially intact cardiovascular system, and what exactly happened in the preoperative phase of the surgery?

According to the literature, in any person, sudden cardiac arrest may be caused by several problems, with cardiological problems taking the leading positions [1]. In neurosurgical patients, asystole may be caused by various reasons as well, but they significantly differ from those that cause sudden asystole in patients with no cerebral disease. In a similar way, acute subarachnoid hemorrhage (ASH) from a cerebral aneurysm may manifest [2]. Moreover, aneurysmal ASH is now recognized as the most common neurological cause of asystole. However, our patients had other neurological pathology.

In patients with epilepsy, the phenomenon of a sudden unexpected death in epilepsy (SUDEP) is described, explaining more than 20-fold higher risk of a sudden death in epilepsy compared to the general population [3]. The main causes of sudden death in these patients are recognized as follows: respiratory depression due to seizures, cardiac arrhythmia, cerebral depression, and autonomic dysfunction. However, our patients did not have epilepsy.

Brain herniation and impaction (into the Bichat’s fissure and foramen magnum) can manifest with asystole on the background of the formation of space-occupying brain lesion. Such situations occur after lumbar puncture that forms a caudal dislocation gradient even if withdrawing a small amount of cerebrospinal fluid [4—6]. Brain herniation causing the cardiac arrest may develop in the cranial direction due to rapid ventricular decompression, as described by C. Bahl and S. Wadwa [7]. In that case, resuscitation was ineffective until the dislocation gradient was eliminated after infusion of saline solution. Perhaps, that situation seems to be very similar to our cases, but with certain restrictions. It is described in more detail at the end of the discussion.

During anesthesia and surgery, neurosurgical patients may show their own specific causes of asystole. One of the most common causes of asystole at the beginning of the surgery in neurosurgical patients with paretic limbs is the use of depolarizing muscle relaxants such as suxamethonium chloride [8—10]. The analysis of a large number of such cases revealed the cause: the administration of a depolarizing muscle relaxant causes asynchronous contraction of skeletal muscles (fasciculation), which results in the potassium release from myofibrils; especially high potassium content is in paretic muscles. The sudden release of such amount of potassium into the blood flow creates favorable conditions for hyperkalemia-induced cardiac arrest. In addition, in this situation, the level of the potassium increase in the blood serum is more significant than the absolute values, which may be normal. At present, this situation is well-known in clinic, the schemes to overcome it are developed (the risk groups for this complication; preliminary administration of the depressing subapneic dose of nondepolarizing muscle relaxants or refusal of their use in general), and it is no longer a serious clinical problem today.

Trigeminocardiac reflex during surgical interventions on the structures of the PCF is likely the most studied (after the massive intraoperative blood loss) situation related to intraoperative cardiac arrest in neurological patients [11—13]. However, the development of trigeminocardiac reflex is also described in the case of transnasal pituitary surgery [14, 15] and various cranio-maxillofacial surgeries [16]. As for the trigeminocardiac reflex, it is characterized by the sudden onset of progressive bradycardia (up to the development of asystole) during surgical manipulations near the trigeminal nerve or its branches. The immediate cessation of surgical manipulations and intravenous infusion of anticholinergic drugs are highly effective, and resuscitation is not required in most cases.

Venous air embolism (VAE) is another possible risk factor of intraoperative asystole in neurosurgery. A classic example of VAE development is neurosurgical interventions on the PCF structures or occipital lobes, with a patient placed in the sitting position [17—20]; however, in the literature, there is a series of publications describing the development of massive and even fatal VAE during spinal neurosurgical interventions, with a patient being in the lying position [21—23]. Acute massive VAE can actually cause asystole, but its development is related to damages to large venous collectors with rigid walls preventing the collectors to collapse if the internal pressure is negative (e.g., cerebral sinuses) and to the presence of a pressure gradient leading the air being sucked into a venous collector. However, all of this does not coincide with our situation.

Reflex asystole directly affecting the vagus nerve is described for carotid endarterectomy, facial nerve plasty, and some other cervical spine surgeries. Severe bradycardia (up to the development of asystole) is a described complication of angioplasty and carotid stenting [24—28]; it can also occur during functional neurosurgical interventions [29]. Finally, asystole may occur at the stage of completing the neurosurgical intervention and be caused by the syndrome of excessive subgaleal drainage [30] or by the spontaneous intracranial hemorrhage in the area of surgical wound, leading to the compression of the brainstem [31]. All the aforementioned
clinical cases occur relatively rare but still they are described in the literature. However, these cases also have nothing to do with our clinical cases.

Finally, the drugs administered during anesthesia and surgery may also cause or stimulate asystole for various reasons. Opioid analgesics (especially opioid full agonists), such as fentanyl, sufentanyl, alfentanil, and remifentanil, can cause bradycardia via the well known central mechanism of vagus nerve stimulation [32]. However, this effect in our clinical situation may be regarded as only a contributing factor. Central alpha-2 adrenergic agonists (clonidine and dexmedetomidine) are regarded as another group of drugs which can cause asystole during surgery. For example, there are enough alarming publications regarding dexmedetomidine [33, 34]. Finally, we have found in the literature a case report on intraoperative asystole after adriamycin cytostatic administration during surgery [35]. However, our patients did not receive these drugs, except opioid analgesics (fentanyl) in relatively small doses.

None of the aforementioned causes of asystole that are described in the literature (except perhaps the herniation and impaction) clarify anything regarding our clinical observations. Consequently, the most likely explanation seems to be as follows. It is known that intubation of trachea is accompanied with a specific hemodynamic effects of varying severity, the so-called pressor response (PR), which is also associated with increased intracranial pressure [36]. It is also known that severe PR is a real risk factor for patients with severe cardiac insufficiency (there is the risk of acute decompensation) and cerebral aneurysms (there is the risk of aneurysm rupture) [37]. This list should apparently include neurosurgical patients with severe intracranial hypertension at the subcompensation and decompensation phases.

On the background of increasing systemic arterial blood pressure under PR, even a slightly increased cerebral blood flow can apparently induce that minimally increased level in intracranial pressure which may cause decompensation of the intracranial system and displacement of certain brain structures. This is evidenced by the autopsy report of the first patient. In addition, vagus nerve stimulation is likely to contribute to the development of asystole in our observations as well. The risk factors for asystole could include the administration of fentanyl (that can cause bradycardia) during induction of anesthesia and the nonuse of anticholinergic drugs during premedication. Despite the fact that the anesthetists took the necessary steps to stop PR in both observations (by applying the adequate dose of propofol, an opioid analgesic, and lidocaine during induction of anesthesia) and the intubation was performed quickly and was nontraumatic, it seems that the intracranial pressure reached that critical level that even slightly increased BP and cerebral blood flow caused the decompensation.

Interestingly, in one of the most large (22 case reports!) published series of clinical cases regarding asystole in neurosurgical patients, five patients had asystole at the stage of induction of anesthesia and at the beginning of the surgery, but still the authors recommend as follows: “… during resuscitation of a neurological patient, it is of particular importance to perform timely measures aimed at reducing the intracranial pressure and preventing edema and brain swelling.” [38].

External ventricular drainage used prior to anesthesia is still likely to be reasonable for patients with pronounced symptoms of occlusive hydrocephalus, especially after acute occlusive hydrocephalus occurring immediately prior to surgery, even if it was successfully stopped by drug administration.

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In the given study, the authors presented their own experience regarding two clinical cases of hemodynamic instability in neurosurgical patients during surgery. Despite the development of pharmacology and the use of modern methods of intraoperative monitoring, the issue of cardiac arrest at various stages of anesthesia remains extremely problematic. For preventing the anesthesia-induced complications, algorithms of preoperative management and examination of the patient are developed and different anesthesia-related risk scales are used. However, even the strict observance of all pre- and intraoperative algorithms of patients’ management does not exclude the possibility of a sudden cardiac arrest.

Clinical cases presented by the authors describe the dramatic events occurring during anesthesia in neurosurgical patients. Despite the different nosology, both cases were appropriately united for a joint analysis of a clinical situation. In both patients, hemodynamic instability and the development of asystole were detected on the background of a stable state favoring. In both cases, hemodynamic instability and the development of asystole were timely and effective, which even enabled continuing the surgery.

Commentary

In the discussion, the authors presented a comprehensive and accurate analysis of the preoperative management of patients and analyzed the possible factors of sudden cardiac arrest. The main possible factors causing hemodynamic instability in patients without cardiac pathology are exhaustively specified. On the basis of clinical data analysis and autopsy reports, the authors concluded that the cause of sudden cardiac arrest was not fully established.


arrest in the presented patients is the pressor response to procedures and then the subsequently increased intracranial pressure and displacement of the brain.

In my opinion, the authors were close to the truth in their conclusions. A few hours before surgery, the patients had episodes of aggravated clinical symptoms of brain herniation, which were effectively stopped by pharmacological methods. The initial cause of patients’ health impairment was likely not so much the pressor response during procedures. In my opinion, placing the patient in the recumbent position in bed and on the operating table during intubation and preparation for surgery was more significant cause. In patients with signs of intracranial hypertension that already occurred due to transfer a patient in the recumbent position, changes in intracranial pressure gradients and disturbance of venous outflow from the cranial cavity may occur, which can induce (along with hemodynamic changes) displacement and impaction of the cerebral structures. Brain herniation was confirmed by the autopsy report of the deceased patient. In the early stages of anesthesia during procedures, a possible solution to the problem could have been measures aimed at the correction of intracranial hypertension, i.e. the patient’s head end should have been raised, hyperosmolar solutions should have been used, and ventricular drainage should have been applied early. (Probably, ventriculostomy and ventricular drainage should have been performed at the very first clinical signs of occlusive intracranial hypertension on the night before the surgery.) Neuroimaging could have probably helped in the decision (CT and/or MRI signs of brain herniation and progression of hydrocephalus). Timely detection of risks of intracranial hypertension and displacement of the brain structures, as well as measures aimed at preventing high intracranial pressure can help to avoid hemodynamic instability at various stages of anesthesia.

In the study, the authors describe a very significant problem in anesthesiology; the article is easy to read, but also requires us to reflect on the way of solving the particular clinical situation. Although the article is relatively short, it includes a detailed analysis of the possible causes of intraoperative cardiac arrest. Given the extensive experience of the authors, I wish them to share more often their priceless observations with colleagues.

The article can be useful not only for anesthesiologists, resuscitation specialists, and neurosurgeons, but also for all specialists involved in the treatment of neurosurgical patients.

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Transartrial and transvenous embolization of deep binodal arteriovenous malformation of the brain

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The multimodal approach to the treatment of arteriovenous malformations yields good results. However, small and deep malformations still pose a big problem for surgeons. Transvenous embolization was designed as an alternative to conventional transarterial embolization in cases when the latter is not available, while macroscopy and radiosurgery are associated with high risk. In this study, we describe one case of surgical intervention through the transarterial and transvenous (for the first time in our clinic) approaches in a 41-year-old patient with a binodal malformation in the subcortical nuclei of the left hemisphere of the brain, which had previously become the source of massive parenchymal ventricular hemorrhage. Transarterial embolization of the thalamic node of the malformation was performed as the first step. After 6 months, transvenous embolization of the hypothalamic node of the malformations was performed as the second step. Successful operation was ensured by using a stable coaxial guiding catheter system with the maximum distal approach and intranidal positioning of a microcatheter with detachable distal portion upon temporary occlusion of afferent vessels of the malformations using a balloon catheter. The operation resulted in total thrombosis of the malformation. No perioperative complications were observed. Control examination in 6 months revealed no evidence of recanalization of the malformation. Conclusions. The transvenous approach can be successfully used in endovascular treatment of small and deep arteriovenous malformations with a single drainage vein, which are inaccessible to direct surgery. It can also be used when radiosurgery is associated with high risk in cases where transarterial embolization is infeasible.

Keywords: arteriovenous malformation, transvenous embolization.

Cerebral arteriovenous malformations (AVMs) are the most common congenital cerebrovascular diseases with high risk of intracranial hemorrhage (2% annually) and mortality (1—1.5%) [1]. Currently, there are three directions in the treatment of this disease: endovascular embolization, microsurgical removal, and radiosurgical therapy [2, 3]. The best results of its treatment with high level of radicality and low rate of disability are reported by neurosurgical centers that use a multimodal approach, combining all three treatments in different ratios to achieve total exclusion of malformations, even those difficult to treat, while minimizing risks and avoiding the limitations of each method.

Despite the significant advances in the treatment of this pathology, small and deep malformations pose a big problem for surgeons, since they are associated with the high risk of intraoperative and postoperative hemorrhage followed by the development of neurological deficit due to damage to functionally important areas.

Transvenous embolization was designed as an alternative to conventional transarterial embolization in cases when the latter is not available, while macroscopy and radiosurgery are associated with high risk. The following is our first experience with this technique in the treatment of a complex deep binodal arteriovenous malformation.

Case Report

A 41-year-old male patient with long (about 20 years) history of headaches suffered a massive parenchymal and ventricular hemorrhage 2 months before hospitalization. At the time of admission to the Neurosurgical Center of the Novosibirsk Research Institute of Circulation Pathology, there were mild general cerebral (periodic moderate diffuse headache) and focal (4/5 right hemiparesis) symptoms.

According to MRI, the malformation in this patient was represented by a binodal vascular mass at the subcortical nuclei of the left hemisphere of the brain. One node was located in the left thalamus near to the posterior wall of the occipital horn of the left lateral ventricle and spread into the ventricular cavity. The second node was located in the left hypothalamus and spread into the cavity of the third ventricle. There were signs of past parenchymal and ventricular hemorrhage (hemosiderin deposition), which originated from the thalamic AVM node.

According to cerebral angiography (Fig. 1a, b), the malformation nodes were separated from each other and had separate blood supply with the same venous drainage. Thalamic AVM node (16×14×9 mm) was supplied from the anterior, posteromedial, and posterolateral choroidal arteries on the left, while hypothalamic node (12×8×7 mm) was supplied from thin perforating arteries of the terminal part of the communicating segment of the left internal carotid artery and the A1 segment of the left anterior cerebral artery.

The hypothalamic node was drained through the thalamostriate vein into the internal cerebral vein, which two thalamic veins draining the thalamic node of the malformation then flow into.
Endovascular treatment was carried out in two stages. First, transarterial embolization of the thalamic node of the malformations was performed, since, according to MRI (Flair mode), it is this node that was the source of bleeding. Six months later, transvenous embolization of the hypothalamic node of the malformation was performed. Both operations were conducted under combined general anesthesia with tracheal intubation. Taking into account the use of balloon occlusion in the second surgery (to prevent thromboembolic complications), systemic anticoagulation was carried out using intravenous bolus heparin (5000 units) to achieve target activated clotting time (about 200 s).

Stage 1 (Fig. 1). Two Envoy 6F guiding catheters (Codman, USA) were installed in the petrous segment of the left internal carotid artery and V3 segment of the left vertebral artery. Three afferent vessels of the malformation (anterior and posterior choroidal arteries) were catheterized alternately with Apollo microcatheters (ev3, USA). Thalamic node was intranidally injected with 3.1 ml of Onyx18 (ev3, USA) to achieve total exclusion of the thalamic AVM node, while maintaining the venous drainage of the hypothalamic node.

Due to the high risk of hyperinfusion intracranial hemorrhage, it was decided to embolize the hypothalamic node at the second stage. The postoperative period was uneventful, the functional outcome scored 1 point on the modified Rankin scale, which corresponds to the pre-operative level.

Stage 2 (Fig. 2). Envoy 6F guiding catheter (Codman, USA) was installed in the petrous segment of the left internal carotid artery, and Chaperon 6F/5F MP /VTR coaxial catheter system (MicroVention, USA) was injected through the left jugular vein to the middle of the left transverse sinus (6F catheter) and then to the distal portion of the direct sinus (5F catheter). Then, Apollo microcatheter (ev3, USA) was placed intranidally to the hypothalamic node of the malformation through the Mirage guidewire (ev3, USA) via the inner cerebral vein and thalamostriate vein. In order to reduce blood flow in the AVM during the injection of the composition, temporary occlusion of A1 segment of the left anterior cerebral artery was performed using HyperGlide 4x15 balloon (ev3, USA) followed by occlusion of the communicating segment of the left internal carotid artery during 2 to 5 minutes. The total duration of occlusion was 15 min. The malformation was embolized totally by injecting a total of 2.5 ml of Onyx18.

Perioperative period was uneventful. Functional outcome corresponded to 1 point on the modified Rankin scale, just as before the operation.

Long-term result of treatment was evaluated 6 months after total AVM embolization. During this period, the patient reported significant decrease in the frequency and intensity of headaches. The functional outcome remained at the level of 1 point on the modified Rankin scale. MRI of the brain (Fig. 3a, b) and direct cerebral angiography (Fig. 3c) detected no signs of AVM functioning.

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**Fig. 1.** The carotid (a, b) and vertebral (c, d) angiograms in the arterial phase, lateral projection.  
a, b – angioarchitectonics of the thalamic node of the malformation with afferents from the left anterior and two posterior choroidal arteries and venous drainage through two hypertrophic thalamic veins into the vein of Galen; c, d – the stages of transarterial embolization of the thalamic node with its gradual total exclusion from the circulation.
Fig. 2. The carotid angiograms in the arterial phase, lateral and oblique projections.

Stages of the transvenous embolization of hypothalamic node of the malformation; a – angioarchitectonics of the hypothalamic node at the time of installation of a microcatheter and balloon catheter; b – injection of 0.8 ml of embolic agents; c – positioning of the endovascular tools; d – injection of 1.2 ml of embolic agent, the balloon catheter is shifted to the communicating segment of the ICA; d – total closure of the AVM.

Fig. 3. 3DTOF MRI (1.5T) with intravenous injection of gadolinium in the capillary phase (a, b) and carotid angiogram in lateral projection (c) 6 months after the final embolization. There is no evidence of recanalization of the malformation.
Discussion


In 2013, Pereira et al. [8] used a balloon catheter in the transvenous embolization for temporary occlusion of malformation afferents. This allowed both preventing non-target embolization of the main vessels and reducing the blood flow through the AVM, facilitating penetration of adhesive composition into the node.

During the period from 01.01.2011 to 01.09.2013, a total of 321 embolization sessions in 173 patients with arteriovenous malformations of the brain were performed at the neurosurgical center of E.N. Meshalkin Novosibirsk Research Institute of Circulation Pathology with a total radicality of 67.1% [9]. The case reported in this paper is our first experience of the use of transvenous access to malformation node. Given a history of hemorrhage from the AVM in this patient, there was a significant risk of re-rupture, which is an absolute indication for surgical treatment. During the initial planning of its tactics, direct surgical intervention was obviously impossible due to AVM location. Radiosurgery was also considered to be unsuitable due to the large total size of malformation nodes (which exceeded the limit of this method of 3 cm) and high risk of damage to functionally important brain structures. Thus, endovascular technique was the method of choice in this case.

When closing the thalamic node of the AVM, transarterial embolization technique with Onyx was applied with intranidal catheterization of the AVM node, which enabled total exclusion of this node in one step.

In view of the fact that the hypothalamic portion of the malformation filled through thin perforants of the terminal part of the communicating segment and A1 segment of the left anterior cerebral artery, transarterial catheterization proved to be technically impossible, since the diameter of these afferents was below the minimum diameter of the catheter. However, the features of AVM angioarchitectonics (small-sized malformation node and draining through a single vein) enabled transvenous embolization with minimal risk to the patient. The use of coaxial system helped to achieve stable position of the working guiding catheter and improve the manageability of the microcatheter for safer and more efficient catheterization of the malformation draining vein. Additional conditions for total exclusion of AVM were provided using the technique of temporary balloon occlusion of the vessels carrying afferent branches during the injection of the adhesive composition.

Summary

Transvenous approach is rarely used in treatment of arteriovenous malformations and can not be recommended for routine use due to the high risk of hemorrhagic complications. However, there are situations where transvenous embolization has some chance of success. Indications for its use include small size of malformation node, single draining vein, infeasibility of catheterization of afferents of the malformation (small diameter and significant tortuosity), and high risks of microsurgery and radiosurgery.

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The authors presented a very interesting observation based on the use of combined approaches in the endovascular treatment of a deep binodal AVM. Application of the transarterial approach in the endovascular surgery of AVM is nowadays a standard approach in occlusion of malformation stroma. However, arteriovenous malformations often have multichannel blood supply with numerous small afferents, which are inaccessible to catheterization. Moreover, partial or subtotal embolization of AVM can lead to increased risk of rupture (re-rupture) of AVM.

The authors describe the technique of simultaneous multicatheter method in AVM embolization (consisting of three vascular beds) with non-adhesive liquid composition. As a result, total embolization of the first AVM node (the source of hemorrhage) was achieved. Then, as a second stage, the authors used transvenous approach to the stroma of the second (silent) AVM node and conducted its total embolization, while afferents were temporarily occluded with a balloon catheter. As a result, the authors succeeded in two-staged radical treatment of the complex AVM using endovascular technique.

Commentary

It should be noted that the second stage of surgical treatment was associated with high risk of intraoperative and postoperative complications, especially if total occlusion of AVM node had not been achieved in the case of unintended occlusion of a single draining vein. In this situation, radiosurgical treatment might be the method of choice as the second phase, since it is associated with lower risk of complications. At the same time, this work demonstrates the capabilities of modern endovascular neurosurgery in the treatment of AVM, while the absence of complications is indicative of high professional level of the surgeon and the entire medical team.

However, this technique can not be recommended as the routine method of AVM embolization. Implementation of this manipulation is justified only in rare cases, in accordance with the features of AVM angioarchitectonics described by the authors, at a specialized clinic.

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New Surgical Treatment for Vertebral Artery Pseudoaneurysms at the Boundary between the $V_2$ and $V_3$ Segments

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The clinical case of a patient with a pseudoaneurysm of the left vertebral artery at the boundary between $V_2$ and $V_3$ segments after a stab wound to the neck is reported. The patient underwent a rare variant of surgical reconstruction of the vertebral artery, including resection of the vertebral artery pseudoaneurysm at the boundary between the $V_2$ and $V_3$ segments, the vertebrovertebral autovenous shunting (from the $C_6$ vertebra to the $C_5-C_6$ vertebrae with resection of the anterior wall of the vertebral artery canal). Postoperatively, SCT angiography revealed satisfactory blood flow in the shunt and improvement of the neurological status. The article provides a literature review on surgical procedures at the distal portion of the vertebral artery. The surgical technique was illustrated (intraoperative photos), demonstrating that the vertebral artery can be easily mobilized at any part of the $V_2$ segment with minimum damage to the adjacent tissues.

Keywords: vertebral artery, false aneurysm, autovenous bypass.

Vertebral artery (VA) is a paired vessel of the vertebrobasilar system and supplies functionally different parts of the central nervous system with blood, from the spinal cord to the cerebral cortex. All kinds of its impairment cause polymorphic clinical presentation of the disease. Symptoms of circulatory disorders and localization of the foci depend on the location and extent of VA lesion. The circulation disorders may be asymptomatic when there is sufficient blood flow compensation even following occlusion of one vertebral artery.

Lesions of VA are most often characterized by slow manifestation of symptoms and progressive course with prolonged recurrence. When extracranial parts of VA are impaired ($V_1—V_3$ segments) the following symptoms are observed: vertigo; tinnitus with hearing deterioration; violation of statics and imbalance (on the side of lesion), phonation and swallowing; dysarthria, diplopia, nystagmus, visual disturbances, and gaze paresis. Spastic paresis or paralyses develop on the side opposite to the occlusion (rough stenosis). Various types of Wallenberg-Zakharchenko’s syndrome and symptoms of the arteries impairment in the basin of the medulla oblongata are manifested when there is thrombosis or stenosis of $V_4$ (intracranial) segment of VA.

Arterial aneurysms (AAs) are a type of disorders in VA, which is fortunately quite rare. While $5—15\%$ [1, 2] of all cerebral aneurysms are located in the vertebrobasilar pool (VBP), the share of only $1\%$ of intracranial aneurysms affect the VA itself. Only $0.4\%$ of these can be cured surgically [1]. Aneurysms of VA at the pre-hemorrhage stage are often asymptomatic or occur as a tumor of the posterior fossa. The clinical presentations of VA aneurysms are manifested in symptoms of VII—XII cranial nerves disorders and cerebral symptoms. As a rule, etiology of vertebral artery aneurysms is either traumatic or dysplastic and is rarely post-infectious.

The world literature describes only a few publications devoted to the description of vertebral artery aneurysms in the extracranial segments. To date, the greatest number of cases (12 cases) of aneurysms of the extracranial portion of VA was presented by R. Berger, who described patients with Ehlers-Danlos and Marfana diseases, and AAs of both vertebral arteries was observed in 7 cases [3].

The most diverse surgical tactics have been proposed over the past 30 years, but the $V_3$ segment of the VA was necessary to be involved. The possibility of bypass from the distal vertebral artery for VA occlusion was reported for the first time in 1977 by A. Carney et al. [4]: they performed the first autogenous vein bypass (AVB) from the common carotid artery (CCA) to the distal vertebral artery. In the same year, G. Corkill et al. [5] used the external carotid artery (ECA) for shunting from $V_3$ segment of VA. In 1978 A. Carney et al. [6] reported the opportunity of carotid distal vertebral artery bypass for carotid artery occlusion at $C_{3-4}$ level. B. George and C. Laurian [7] in 1979 improved the approach to $V_3$ segment of VA and used it for clipping the aneurysm of VA at $C_{3-4}$ vertebra with the creation of anastomosis between subclavian artery and distal vertebral artery at $C_{2-3}$ level. In 1981, G. Besson et al. [8] presented two observations with different types of external carotid-distal-vertebral autovenous shunting and A. Carney et al. [9] described the use of well palpable $V_3$ segment loop of VA at $C_{3-4}$ with anastomosis to ECA and that a hypertrophic occipital artery may be directly anastomosed to the vertebral artery.
R. Spetzler et al. [10] in 1987 reported on the possibility of an occipital-vertebral anastomosis to \(V_3\) segment atlantic part of the VA at extravasal osteophytic compression of the vertebral artery at \(C_1—C_2\) level. S. Mabuchi et al. [11] in 1993 used radial artery graft from external carotid artery to atlantic part of vertebral artery for the first time for a case of dissection of the extracranial vertebral artery at \(C_1—C_2\) level. Finally, in 2013 K. Hisashi et al. [12] described three clinical cases of aneurysms of \(V_4\) segment intracranial part in patients, who were subjected to the vertebrovertebral autovenous shunting from \(V_2\) to \(V_4\) segment of VA after resection of aneurysms in 2 cases and to the internal carotid vertebral shunting in 1 case using radial or occipital artery grafts.

We offer a rare option of surgical reconstruction of VA, including resection of the vertebral artery pseudoaneurysm at the boundary between the \(V_2\) and \(V_4\) segments, the vertebrovertebral autovenous shunting. The operation has been performed for the first time in the world in a patient after a stab wound on the left side of the neck and left vertebral artery pseudoaneurysm emergence at \(C_2—C_3\) level. We present our own clinical observation.
Case description

Patient Sh., aged 39, received inpatient treatment at the Department of Neurosurgery, Central Military Clinical Hospital n.a. A.A. Vishnevsky, from June 2, 2014 to June 10, 2014 (medical record No. 15278). Medical record: trauma of February 21, 2014, unknown stabbed in the neck in the region of the upper third of the neck on the left. The patient received primary surgical wound cleaning at the place of residence and then inpatient treatment (February 25, 2014 to March 21, 2014) at the Department of Neurosurgery of Ambulance Hospital on the diagnosis of concomitant injury, stab wound to the neck on the left with injury to the external jugular vein, the sternoclidomastoid muscle, spinal cord with development of Brown-Sequard’s syndrome on the left, disorders of pelvic organs of the central type, vertebral spinal cord injury, and right-sided anterior atlas subluxation. The subluxation was repositioned by hand according to the Ryushe-Guetter’s method. Conservative therapy showed a positive effect: pain attenuated, hypoesthesia area regressed significantly, and the function of the pelvic organs restored. Continued conservative outpatient treatment had a positive effect: impaired sensitivity in the left extremities regressed fully, and grade of hypoesthesia in the right extremities decreased considerably. Magnetic resonance imaging of May 26, 2014 (Fig. 1) revealed focus of post traumatic myelopathy at C_{II}—C_{III} level (6×7×3 mm) and a 22×19×18 mm large lesion with clearly defined and irregular contours (pseudoaneurysm) was found in the...
projection of the left vertebral artery at C_{II}—C_{III} level (Fig. 2). The patient was hospitalized in a planned manner to perform angiographic examination and surgical treatment. The diagnosis of a pseudoaneurysm was confirmed by angiography of June 3, 2014 (Fig. 3).

**The surgical procedure.** The anterolateral approach at the anterior surface of the sternocleidomastoid muscle to the vessel-nerve bundle of the neck was employed (Fig. 4). After mobilization of the wounded internal jugular vein (IJV), the accessory nerve was divided distally, which crosses the internal jugular vein obliquely. In projection, the area of their crossing corresponds to the C_{I} vertebral transverse process, which was easily identified by palpation and was the upper point of approach. Afterwards, anterior bundles of the levator scapulae were divided and retracted between C_{I}—C_{II} vertebral transverse processes exposing the anterior C_{II} branch of the spinal nerve, which branches into two. Vertebral artery was identified under the spinal nerve and mobilized; anterior branch of C_{II} of the spinal nerve and VA were kept with handles (Fig. 5).

At the second stage, VA below the C_{III} level was mobilized and the anterior wall at the transverse process of the C_{IV} vertebra was resected using pistol forceps and VA prior to exit from canal at C_{V} level was divided (Fig. 6). Meanwhile, on the left leg great saphenous vein
with a length of 15 cm was detached and prepared for shunting.

At the third stage, distal vertebral artery was stitched, secured and cut after its exit from the CII vertebral process and attached to preliminary prepared autovein by an end-to-end distal anastomosis (Fig. 7). Blood flow re-establishing showed that the anastomosis was successful.

At the fourth stage vertebral artery proximal of its entry to the transverse process of the vertebra CIII was stitched, secured and cut and end-to-end anastomosis to the autovein was created (Fig. 8). Blood flow was re-established and the anastomosis was successful (Fig. 9). Bleeding was absent when the aneurysm cavity was opened (Fig. 10).

The postoperative period was without complications. The wound healed by primary intention. Mild cerebral symptoms regressed and showed improvement of the neurological status, asthenia decreased.

In the early postoperative period spiral computed tomography (SCT) angiography (of June 6, 2014) demonstrated the region of a functioning autovenous shunt (Fig. 11).

**Conclusions**

The methods of surgical management of arterial aneurisms of VA in V2, which were previously proposed in the world literature, did not afford complete exclusion of the aneurysm from blood flow, since collateral arterial arcs connecting VA with the anterior spinal artery maintained that subsequently did not guarantee absence of various complications, including fatal.

We believe that the choice of the described surgical treatment tactics is the most successful due to that natural patency of VA restores and simultaneously functioning pseudoaneurysm is resected. Moreover, the surgical method demonstrates that the VA can be easily mobilized at any region of the V segment with minimal traumatization of the long muscles of the neck. In the future, at spondylogenic lesion of VA technique can be easily applied to restore sufficient blood flow through the VA without the use of complex vascular reconstructions in the V1 or V3 vertebral artery segments.

**REFERENCES**

The presented clinical case of a pseudoaneurysm of the vertebral artery in a patient after a stab wound in the neck is a rare case, and the problem of surgical intervention on the vertebral artery is evident. In patients with aneurysms of VA, vertebrobasilar insufficiency takes the first position among the clinical manifestations characterized by vertigo, cerebellar ataxia, rarely lesion of VII—XII cranial nerves in pseudotumor course of the disease and vertebral basilar ischemia, usually arising as a result of microembolism of cerebral arteries.

The incidence of arterial aneurysms of VA, including the intracranial segments, is less than 1% of all aneurysms of brachiocephalic arteries. There are only a few publications in the literature on the surgical treatment of aneurysms of the extracranial vertebral artery segments and the surgical interventions described in the literature for pseudoaneurysms of the extracranial vertebral artery segments were applied with obligate use of traumatic approach to V3 segment of VA and did not afford exclusion of the aneurysm from the main blood circulation, which in turn contributed to risks of thromboembolic complications in the brain in the postoperative period.

The authors analyzed in detail the literature on this subject, the main surgical methods of reconstruction of vertebral artery have been described, and the advantages and disadvantages of different surgical techniques have been considered.

In this clinical case, for the first time a rare type of reconstruction of the vertebral artery with a pseudoaneurysm exclusion from the blood flow was proposed — the vertebrovertebral autovenous shunting distally and proximally to the lesion area using an autovenous graft with proximal and distal end-to-end anastomosis. There has been a convincing result in the early postoperative period confirmed by SCT angiography of brachiocephalic arteries and improvement of neurological symptoms in the patient.

The authors described in detail the operation procedure; the article is well illustrated with intraoperative photographs to facilitate the perception of the submitted material. The possibility of mobilizing the vertebral artery at V2 segment using the anterolateral approach with minimum damage to the adjacent tissues has been shown. The undeniable advantage of the chosen technique of reconstruction is resection of the aneurysm from the main blood flow with elimination of the risk of thromboembolic complications in the brain in the postoperative period.

Lack of follow-up and individual observations do not allow to fully talk about the safety and efficacy of this procedure, as the long term evaluation of the results was not carried out.

Unfortunately, the authors did not focus on the anatomy of other brachiocephalic arteries; in particular, the efficiency of the circle of Willis in posterior and anterior circulation was not assessed. It is also not clear whether the examination of the brain was carried out to exclude post-ischemic changes in the vertebrobasilar basin, which could well be a partially cause of the indicated symptoms in patient. The description of the operation procedure does not contain the information on the anticoagulation protocol and antiplatelet therapy used in the perioperative period, the procedure of removing the forceps and measures for the prevention of distal embolism at re-establishing blood flow in the vertebral artery. Meanwhile, this information is very useful for practicing surgeons. All this does not diminish the practical relevance of the information provided.

The surgical procedure can also be useful in other types of lesions of vertebral arteries (spondylogenic compression, pathological deformation) and thereby indications to the autovenous grafts of extracranial vertebral artery may be extended. Without a doubt, this work is extremely useful and interesting for those engaged in reconstructive operations on the brachiocephalic arteries.

D.Yu. Usachev (Moscow, Russia)
Isaak Savel’evich Babchin is a true patriarch among fellows in the great field — founders of national neurosurgery! He lived a long life of almost 94 year. Getting older physically, he kept his powerful intellect to the last days. How wise and critical was his reply at his 90th anniversary at the Polenov Institute!

Isaak Babchin was not only a highly respected but also very well-liked person. This is why all famous Soviet neurosurgeons gathered for the anniversary celebration in Leningrad in June 1985. I remember that when I along with A.N. Konovalov and E.I Kandel’ went to a market for bouquets, salespeople who learned of the person for whom the flowers were designated did their best because they also heard about the wonderful surgeon Isaak Savel’evich Babchin.

The celebration was vivid and memorable. Warm speeches invariably ended with sincere wishes to I.S. Babchin to live to the 100th anniversary. Then, Isaak Babchin hardly stood up: “Why do you hate me so much? I am almost blind, deaf, and barely moving. And you wish me more 10 years of this life”. At that moment, everyone felt uncomfortable and sad.

Isaak Babchin was a brilliant orator. The audience always hung upon his lips. How fascinating his lectures were, how warmly and gratefully he gave the ultimate send-off to his colleagues! I remember his farewell words at the memorial service for A.I. Arutyunov: “The last brightest star in the Burdenko constellation is set”.

Isaak Babchin’s oratory was complemented by imaginative gestures; he widely spread his arms, as if he had disembosomed himself to people and embraced them. This Babchin’s embrace demonstrated the good nature of a talented person...

...I first saw Isaak Babchin when I was a graduate student. He had came both to the Institute and to conferences. This short man with the bald head and rounded figure immediately prepossessed to himself by his friendliness, exceptional kindness, and gentleness. His judgments were deep and wise; both masters and young neurosurgeons carefully listened to him. When I happened to listen to Isaak Babchin, I was excited both by his thoughts and by their imaginative embodiment.

Accomplishment and achievements

I had learned the biography of Isaak Babchin long before I made friends with him. He was born in Vilno in the family of a merchant of the first guild in 1895. This gave him the right to live beyond the Pale of Settlement. So, Isaak Babchin moved to St. Petersburg (Petrograd) where he became a student of the Psychoneurological Institute in 1914. His study was interrupted by World War 1. He was mobilized and served a common soldier in the Imperial Army from 1915 to 1917 and then an associate doctor in the Red Army. After the war, he completed his medical education at the State Institute of Medical Knowledge where his devotion to surgical neuropathology started. His teacher was A.L. Polenov who prophetically wrote: “...I think that he (I.S. Babchin. – L.L.) will undoubtedly be a prominent surgeon-neurologist, a specialist in a new field, which counts just a few scientists in the USSR”.

In 1924, I.S. Babchin was a resident at the Institute Traumatology, and then he became the head of the Neurosurgical Department. In 1935, Isaak Babchin defended his doctoral thesis on “Clinical picture and surgery of cervical spine tumors”.

Since the establishment of the Leningrad Neurosurgical Institute (1938), Isaak Babchin became the deputy director for science and the head of the Clinical Department. Here, his bright many-sided talent of an organizer, diagnostician, neurosurgeon, scientist, and educator blossomed.

Isaak Babchin was one of the founders of pediatric neurosurgery: he established the Children’s Department at the Polenov Institute where he developed and improved a number of surgical techniques in the field of pediatric neurooncology. Stereotactic surgery for parkinsonism and hyperkinesias was developed under his guidance. He splendidly mastered analgesic surgeries on the trigeminal nerve roots and spinal tracts.
The great merit of I.S. Babchin, together with A.L. Polenov, was the creation of the first domestic guide “Fundamentals of practical neurosurgery” (1943).

**Chief front neurosurgeon**

Wars broke out: first, the Finnish War occurred; then, the Great Patriotic War started. Isaak Babchin was appointed the chief neurosurgeon of the Leningrad Front. In the besieged city, he organized specialized care to warriors with head and spine wounds. Under bombings and artillery bombardments, he tirelessly conducted surgeries for the most complex gunshot injuries to the nervous system.

E.I. Stroganova, an Isaak Babchin’s student, writes about his most difficult period of life during the Leningrad Blockade: “In the first months, the hospital staff (evacuation hospital 1015 – L.L.) consisted of doctors from the Ott Institute and junior doctors who completed the 4th year of the 1st Medical Institute (Leningrad – L.L.) and were drafted into the army.

I.S. Babchin had to manage the problem of retraining these doctors to neurosurgeons. He believed that it would be easier to teach neurosurgery to undereducated doctors than to retrain experienced professionals.

Despite of being very busy with providing care to the wounded, Isaak Babchin was standing at the operating table for several hours each day. He began training of wartime neurosurgeons.

He selected only young, undereducated doctors as assistants. During surgery, he explained them in detail all the intricacies of dealing with the brain at different stages of operation. Isaak Babchin daily did the rounds of all departments and attended dressings and other procedures.

While working, he made all comments and recommendations in a very friendly and delicate manner, always out of the ward.

When there was no massive influx of the wounded, he gave trainings on both wartime and peacetime neurosurgery. The studies were usually held in the evening, in a dark and cold room (Leningrad Siege period).

The only visual aid was a cigarette in his hand (he did not smoke), by which he illustrated not only curves but also more complex pictures. He never set exams.

Isaak Babchin worked very, very much. He did the rounds of all departments every night, and at 8 am he held grand rounds with an analysis of the work done over the past day.

In one of these grand rounds, a wall clock fell 3 meter down (due to vibrations during the bombing) and, by a lucky chance, touched only his hand, not his head; but Isaak Babchin continued his lecture without interruption.

Isaak Babchin was an example in all things for young doctors. Even in the most difficult times, he was not broken by hunger and cold, lack of water, and so on. He was always smart; a military uniform was always clean and even elegant; the undercollar was clean and snow white, boots shone. He was always shaved.

Isaak Babchin very cherished his colleagues. Even the head of the hospital could not draw out any of the Babchin’s staff, not only doctors but also nurses, without his consent. He was very thoughtful of employees and subordinates. If there was free evening time, he made (delicately) the staff go outside for physical exercises, which was very important and necessary at that time.

Along with others, he went to unload wood, which was delivered to the besieged city by barges through the Neva River. At the initiative of Isaak Babchin, night conferences were held in 1942—1943 where the experience of treatment at various stages of evacuation was summarized. These conferences were attended even by doctors from health support battalions located in the battle line as well as by employees of the Neurosurgical Institute.

All young doctors were given the theme of scientific generalization of experience in treating head and spine wounds and peripheral nerve injuries. These studies and conference proceedings were generalized and published in collections (currently, they are available at the Museum of Leningrad Defense).

Wounded soldiers and officers respected and loved (very loved) Isaak Babchin. He received a lot of letters from the front with gratitude for restored health. Isaak Babchin was a great diagnostician, which is well known to everyone.

After the war, Isaak Babchin did not leave his students. He employed many of them to the Institute, continued to take care of them, and helped them become professionals.

Throughout his life, Isaak Babchin proved himself as a true patriot of his country as well as a great doctor and scientist respected by all who knew him”.

As a major specialist and practitioner of field neurosurgery, I.S. Babchin participated in meetings that were regularly held by the chief surgeon of the Red Army N.N. Burdenko. The facts demonstrate that Isaak Babchin could disagree with N.N. Burdenko. Despite human softness, Isaak Babchin was firm and principled in scientific matters. In particular, when discussing the instructions, he did not approve too widespread use of intracarotid administration of antibiotics and sulfonamides in battle line conditions. N.N. Burdenko blew up and began to ignore I.S. Babchin. However, despite the anger of the three-star general was unpleasant, it did not lead to any restrictions in the professional activity: N.N. Burdenko was not a mean person.

**Post-war drama**

The much more dramatic period occurred in Babchin’s life when he became one of the first in the Soviet Union who was engaged in psychosurgery. He invented an original leucotome and successfully used it for lobotomy in severe chronic forms of schizophrenia, which were not amenable to conventional treatment. However, harassment of cosmopolitans began at the end of the 1940s. On this wave, the frontal leucotomy opponents achieved the ideological defeat of
psychosurgery and its adherents (A.S. Shmar’yan, I.S. Babchin, M.A. Gol’denberg, R.Ya. Golant, and others) at the Scientific Council of the USSR Ministry of Health. Soon, the Order of the Minister of Health of the USSR (December 1950) was issued, according to which psychosurgery was banned, and scientists developing methods of psychosurgery operations were fired.

Isaak Babchin was removed from the position of deputy director for science of the Polenov Institute. In January 1953, when the odious “Doctors’ Case” blew out, he was expelled from the Leningrad State Institute for Advanced Training of Physicians (SIATP) where he headed the Department of Neurosurgery. How the outstanding neurosurgeon Isaak Babchin experienced this, only he knew.

Stalin died, the repressive regime weakened, tension in the society was calmed. However, the published biographies of the scientist as well as his autobiography are silent on this period of persecution and injustice, as if they had never existed. And so it appears in the biographical data: “he headed the Department of Neurosurgery of the Leningrad SIATP from 1947 to 1969” — one might think there was no interruption.

The Thinker

Isaak Babchin was a thinker and, therefore, took up the issues of neurosurgery that required high intelligence. He developed the clinical and pathogenetic classification of closed craniocerebral injury, the main principles of which are not obsolete yet.

He is perhaps the first domestic neurosurgeon who drew attention to the danger of devotion to the technicism, despite all its might. A.I. Arutyunov opposed I.S. Babchin, reproaching him in the methodological backwardness. Note that both masters “fought” in the Journal of Neurosurgery; therefore, their discussion enriched minds of domestic neurosurgeons. Similar discussions have not been held in my favorite journal for a long time.

My friendship with the Master

I developed personal relationships with Isaak Babchin through the book “Traumatic intracranial hematomas” written by me together with L.Kh. Khitrin. I knew Isaak Babchin from his lectures and speeches at conferences, monographs, and articles. Lev Khitrin attended an advanced improvement course in neurosurgery for doctors at the Leningrad SIATP in 1961 and admired lectures and clinical reviews by I.S. Babchin. Once, we received the author’s copies, we immediately sent out the book with an inscription to Isaak Babchin. He wrote back a large warm letter urging further research.

This gave me the opportunity to enter into the correspondence and then enter into the house of the dear master. In their apartment on the 8th Sovetskaya Street with lots of books, paintings, sculptures, and antique furniture, Irina Babchin, wife of Isaak Babchin, hospitably offered me tea. I was fascinated by this rare opportunity to talk to the master in the home environment and experienced an unusual rise because of my interest in the history of neurosurgery. Isaak Babchin behaved naturally, talked at length about himself, and answered even very “thorny” questions. I first became aware of the obstacles he had had to overcome.

Since then, I had visited Isaak and Irina Babchin during my work trips to Leningrad for many years. Isaak Babchin was critical of himself and his current capabilities, but I could persuade him into writing memoirs and thoughts on neurosurgery and contemporary neurosurgeons.

“Idle thoughts of a pensioner”

Irina Babchin, after death of Isaak Babchin, handed me to the Museum of the Institute of Neurosurgery some materials on the work of her husband (including a work copy of his leucotome) as well as his last manuscripts. Here are some excerpts from his “idle thoughts of a pensioner”.

January 1981:

“The second half of the XXth century in our country is characterized by complete employment and the absence of idles, abundance of pensioners, and high alcoholism in the population”.

“A contemporary researcher or scientist is characterized in most cases by a narrow specialization, limited amount of knowledge, and lack of erudition, culture, and sense of humor”.

“Modern multiple co-authorship in science, including medicine and neurosurgery, is sometimes necessary (inevitable) and helpful, although it is unnecessary and even harmful to the scientist in most cases. A real invasion of “co-authors” of scientific articles in academic medical journals, who are often people clinging to the tails of other people’s ideas and works, demoralizes young scientists and impersonalizes them and even the science itself”.

“The situation of a pensioner, especially untimely and protracted, is not only painful but also humiliating”.

“Under normal circumstances, people are entitled to a courteous and diligent attitude. Personally, I have from long ago made it a rule to greet the first my friends on meeting, regardless of their age and social status. I congratulate the first (on New Year and other major holidays and events) my relatives, old friends and co-workers, and my former students and colleagues; however, the number of old friends and comrades is getting less, and many of students have become outstanding scientists: professors, honored science workers, Heroes of Socialist Labor, etc. In this way, I strive to maintain kinship, friendship, and companionship feelings that disappear and fade over the years. I am sincerely pleased that in response to my attention and congratulations, I receive dozens of response greeting cards, telegrams, and letters informing me about life, condition, and an increase in welfare of these people and their families. I regularly
exchange by congratulations with the only remaining school friend, N.P. Fulikov, and I learned from him that our Petersburg Petrovsky college turned 100 on the 3rd of January (old style). Friendly memory in the minds, if not in the hearts, of good people should be fully supported”.

“A bright, even talented, but unprincipled amoral neurosurgeon, neurologist, or representative of other clinical specialties can not be a professor in the highest sense of the word, teacher, scientist, thinker, undisputed advocate of honor and duty despite the abundance of published works, the so-called scientific works (often in co-authorship), and dissertations; that is the guardian of deontology — the doctrine of the rightness. Ethics, medical ethics, and deontology issues have been discussed by Hippocrates, later by N.N. Pirogov, S.P. Botkin, G.A. Zakhar'ina, then by V.M. Bekhtereva, N.N. Petrova, and now (in the press) by scientists, professors, academicians, and even Ministers of Health (N.A. Semashko, Z.P. Solov’ev). This means that there are problems with morality, even in science”.

The Era in Russian neurosurgery

The Lieutenant Colonel of the Medical Service, I.S. Babchin, had good military awards: the Order of the Patriotic War of the 1st Degree, the Order of the Red Star, and a number of medals.

Prof. I.S. Babchin did not have awards in the peacetime. Even when Academician of the USSR Academy of Medical Sciences, the director of the Polenov Institute, V.N. Shamov put Isaak Babchin forward for the honorary title of the “Honored Worker of Science of the Russian Federation” in 1955, this initiative was refused. The second attempt to award Isaak Babchin with the long time and rightfully deserved honorary title was undertook by Academician of the USSR Academy of Medical Sciences, the director of the Moscow Institute of Neurosurgery, A.N. Konovalov in the early 1980s. However, the Health Minister said that this was impossible, since I.S. Babchin had not worked to that moment. Indeed, regalia do not really matter! But, where is justice?!

Isaak Savel’evich Babchin is an epoch in Russian neurosurgery. One of the founders of domestic neurosurgery, he made an enormous contribution to the formation of neurotraumatology, neurooncology, pediatric neurosurgery, field neurosurgery, and development of neurosurgery teaching.

Isaak Babchin was gone, but he left followers and students and made an impact on several generations of neurosurgeons. Therefore, the memory of this outstanding figure of Soviet and Russian medicine lingers on. The St. Petersburg Association of Neurosurgeons, whose founder he was, was named after him.

Largely through the efforts of his student, E.N. Kondakov, a memorial plaque with a bas-relief of I.S. Babchin was placed on the building of the Polenov Neurosurgical Institute, to the development of which I.S. Babchin contributed so much. It is significant that the plenary session of the 1st Congress of Neurosurgeons of Russia in Ekaterinburg was dedicated to the centennial of the memorable teacher, and also a medal was issued in honor of this event.

Finally, on the eve of the 120th anniversary of the scientist, a comprehensive and richly illustrated book “Neurosurgeon Isaak Savel’evich Babchin” written by his younger son, Aleksandr Babchin, who is also a neurosurgeon was published.

Prof. L.B. Likhterman
Topics to be covered in our next issue

- Treatment of patients with arteriovenous malformations
- Treatment of Lhermitte-Duclos disease
- Orbitozygomatic approaches to the skull base