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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.

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Russian Field Neurosurgery: Historical Milestones (on the Occasion of the 70th Anniversary of Victory in the Great Patriotic War)

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Time keeps slipping away. More than seven decades separate us from the victorious day when silence was brought to the war weary world. And the further away that time is, the more prominent and vivid the heroic feat of the peoples of our country is. Throughout the protracted and bloody war with Nazi Germany, our peoples heroically fought on the front lines, selflessly worked in the rear, and sacrificed their lives and health, giving away everything they had for the sake of the coming victory. According to the refined data, among 50 million victims of World War Two, 27 millions were the Soviet people. Among these people, millions of civilians were killed by the enemy in the occupied territories, tortured at death camps, and thrilled and ruined by hard works. Over 15 millions of our soldiers were killed, captured, and missed. Many millions were wounded during the protracted, hard fought battles on the front lines of the Great Patriotic War (1941—1945).

Great and selfless work of a huge army of medical workers, including a large group of neurosurgeons, invaluably contributed to the unparalleled feat of our people in the past war. Field neurosurgery that develops the topical issues of neurosurgical care to wounded warriors and their echelon treatment during wartime is one of the important fields of neurosurgical science and practice. The need for establishing field neurosurgery as an individual discipline was necessitated by the features of organizational, diagnostic, and therapeutic measures that are taken in the field conditions to treat head and spine injuries.

Field neurosurgery has passed several phases in its development. Since head and spine wound outcomes in the field conditions at the turn of the 20th century (at that time, these wounded warriors were evacuated together with others and treated at general surgical hospitals) were extremely adverse, attempts were taken to bring together these wounded warriors at specialized hospitals. For instance, during the Russian-Japanese War (1904—1905), a Russian surgeon O.M. Kholbek arranged evacuation of the wounded with gunshot head injuries to a hospital situated near the front and treated them there after initial debridement. The results of his activity proved to be quite encouraging. His monograph “On Field Head Wounds” published in 1911, which was based on his own extensive observations, provided valuable information on the classification of head injuries, clinical signs, indications and techniques of initial debridement, and complications and outcomes, which have retained their practical importance till present.

During World War One (1914—1918), N.N. Burdenko tried to establish, near the Polish town of Żyrardów, a collector of hospitals, each of which was specialized in certain wound localizations, including head wounds. By the war end, a famous neurosurgeon Harvey Cushing who served in the US Army Medical Corps established a hospital for neurosurgical patients; however, a small number of patients treated at this hospital did not allow any significant generalizations to be made.

In the years immediately before the Great Patriotic War, the armed forces of our country saw action at the battle of Lake Khasan (29.07.1938—11.08.1938), at the battle of Khalkhin Gol (11.05.1939—16.09.1939), and in the Soviet-Finnish war (30.11.1939—13.03.1940). Although those events were local armed conflicts, they were the first serious battles since the times of the Allied Intervention in Russia (1918—1921) and the Russian Civil War (1917—1922) for the scope of participation of new military branches. In these battles, the Red Army gained valuable combat experience. The medical experience gained by the field medical service and, particularly, field neurosurgery, was even more valuable. It was the time when the system of specialized medical care to wounded neurosurgical patients originated, which was developed and implemented in practice in severe conditions of the Great Patriotic War. The system was based on the management of specialized hospitals for patients with head, neck, and spine wounds, located in the army rear and detached with groups of specialists (neurosurgeons, maxillofacial surgeons, ophthalmologists, and otolaryngologists), where the wounded of an appropriate profile were transferred from forward field evacuation points.

Before the beginning of the Great Patriotic War, the fraction of gunshot head wounds in the total number of all war injuries was as follows: 2.7% at the battle of Lake Khasan, 3.6% at the battle of Khalkhin Gol, and 4.7% in the Soviet-Finnish war. This indicator was varying during the Great Patriotic War: it was low for trench warfare and became higher for offensive warfare and pursuit of the defeated enemy. For the entire war period, the indicator amounted to 7—13% of all wounds,

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with 28.1% of wounds being penetrating. Meningitis (10.8%), cephalopyosis (12.2%), and meningocerephalitis (13.3%) were the most common and severe complications.

Specialized surgical care was first established for those who were wounded in the head, neck, and spine, and later for those with injuries of vision, hearing, and jaws. For this purpose, mobile field surgical hospitals were staffed up with appropriate groups of specialists from an independent company of army medical augmentation. Cooperative work of surgeons from related fields provided appropriate care to the wounded with associated and combined injuries.

Proximity of head injury specialized mobile field hospitals to the troops limited surgical care to these wounded at division medical points and first-line mobile field surgical hospitals, providing it only in cases of life-threatening aggravations, including bleeding, shock, asphyxia, and increased brain compression. This tactics of surgical care for cerebral wounds resulted from analysis of the specific features of wounds and combat environment. The fact of relatively slow development of brain tissue infection enabled relocation of a head injury primary surgical care center to specialized army hospitals that were in a better position to provide throughout examination and subsequent, if necessary, hospitalization of the wounded.

Describing the development of Russian field neurosurgery, the topical issue of care in the case of injuries to the peripheral nerve trunks should be particularly emphasized. “Those who dealt with nerve trunk injuries know how slowly and poorly their function is restored, what tortures are associated with the scar formation, and how often the wounded remain disabled and suffering for the rest of their lives”1, — said Nikolay Pirogov to demonstrate the clinical severity of conditions and failure to treat them at that time.

Studies conducted under guidance of P.K. Anokhin, N.N. Burdenko, B.S. Doynikov, A.P. Polenov, and V.N. Shevkunenko before the Great Patriotic War were dedicated to elucidating the mechanism of pathological changes associated with peripheral nerve trunk injuries as well as to searching for rational methods of their treatment. They ensured accumulation of significant scientific and clinical material, and yet “all details of the complicated issue of treating gunshot injuries of the peripheral nerves were revised in the years of the Great Patriotic War”2 (S.S. Bryusova). A scientific and practical classification of peripheral nerve injuries was developed. Each classification group had its features of the clinical course, characterized by certain treatment tactics, and treatment duration, outcomes, and complications.

Studying the wound morphology, reparative and regenerative phenomena in the central and peripheral segments of the injured nerve provided deeper understanding and assessment of the advantages of various treatment methods. In particular, the results of studying the regenerative processes in injured nerves allowed making a conclusion that “a rather complicated problem of closing extensive defects in patients with the injured nerve trunks cannot be considered resolved and requires further investigation”3 (B.S. Doynikov).

Apart from a pronounced specificity of the regenerative processes in injured nerves, the war experience clearly revealed a number of characteristic features in the clinical picture and diagnosis of these injuries. For example, evaluating long-term treatment outcomes, B.G. Egorov noted that failure of the conservative treatment or neurolysis in some cases was likely to be the result of erroneous indications for surgical treatment. In this case, referring to the analysis of sample data from medical histories, he deemed it advisable to extend the list of indications for surgery: “Where neurolysis was ineffective, suturing the nerve may be successful. Where conservative treatment was ineffective, either neurolysis or suturing may be effective, depending on what is found on the surgical table”4.

The experience of military surgeons gained in the war period showed that diagnosis of nerve injuries within first days and weeks after wounding may be quite difficult. According to K.A. Grigorovich who analyzed medical histories of wounded warriors, nerve injuries were diagnosed concurrently with fractures of the hip (shank, forearm, shoulder) in 26.8% (28.5, 33.9, and 42.3%, respectively) of the wounded within the first month, and in 59.8% (58.7, 33.9, and 37.9%, respectively)3 of the wounded within the third month and later. This problem was discussed in August of 1942 at the VI Plenum of the Academic Medical Council under the head of the Chief Sanitary Department of the Red Army E.I. Smirnov who demanded significant improvement in the diagnosis and treatment of peripheral nerve injuries.

The Great Patriotic War was the most important phase in the development of national field neurosurgery that was characterized by establishment of the edifice and effective, scientifically grounded system of neurosurgical care to the wounded in accordance with the specific military and medical situation. During the war, along with the organizational establishment, field neurosurgery was enriched with new theoretical concepts and new

diagnostic and treatment methods, which undoubtedly ensured further development of medical science and improvement of the level and efficacy of medical care in the army.

People make history. Hence, concerning the establishment and development of national field neurosurgery during the Great Patriotic War, one should thankfully remember those who led Soviet field neurosurgery in those hard times and who laid the foundation for its today’s achievements. The outstanding Soviet neurosurgeons N.N. Burdenko, V.N. Shamov, A.I. Arutyunov, A.A. Arendt, B.G. Egorov, L.A. Koreysha, B.A. Samotokin, A.P. Polonov, and others were among these people who gave their talent, energy, knowledge, and efforts to this important area of field medicine.

The format of this article does not allow us to describe all outstanding national neurosurgeons of the Great Patriotic War period. Hence, we will briefly characterize activities of some of them who held chief field surgeon positions in those years.

One of the most outstanding national scientists and neurosurgeons, head of a large scientific school, famous statesman and public figure, laureate of the State Prize of the USSR, Academician of the Soviet Academy of Sciences, first President of the Academy of Medical Sciences of the USSR, lieutenant-general of medical service Nikolay Nilovich Burdenko (1876—1946) played an immense role in managing the activities of a large group of Red Army surgeons during the war. Having become the chief surgeon of the Red Army, since the first days of the war, N.N. Burdenko adhered to the motto: it is not sufficient just to treat a wounded warrior, but the clear management of the entire medical treatment and evacuation support of the troops in the fronts and rear becomes an absolute necessity. He enthusiastically tackled establishing a rational system of surgical care to the wounded and developing the uniform guidelines for surgeons regarding the amount and type of surgical care at different stages of medical evacuation. During the war, he could be seen in the Leningrad front (the north-western direction) and the Western and First Baltic fronts; he took part in the Orel-Kursk operation near Yelets and in combat operations to liberate the Smolensk Region. It should be noted that in the war period, Nikolay Nilovich who had survived several strokes and sometimes not completely recovered after the severe illness, actively participated in work for establishing surgical care in the armies and fronts. This fact, quite characteristic of his personality, serves an example of courageous coping with severe illness for his duty to the country.

It is hard to overestimate the role of N.N. Burdenko in Russian neurosurgery, to the establishment and development of which he dedicated a great part of his titanic efforts. His works in this area became a valuable contribution to the theory and practice of neurosurgery, especially in the field of oncology of the central nervous system, pathology of the cerebrospinal fluid circulation, cerebrovascular disorders, edema and swelling of the brain, plastic surgery of the dura mater and spinal nerve roots, and post-traumatic epilepsy. His following papers are particularly noteworthy: “Surgery for Brain and Spinal Cord Tumors”, “Bulbotomy”, “On the Treatment of Encapsulated Brain Abscesses”, “On Head Injuries”, “Shotgun Injuries of the Skull and Brain”, “Treatment of Shotgun Wounds at the Front during the Great Patriotic War”, “The Modern Issue of the Theory of Wound and Methods of Its Treatment”, “The Characteristic of Surgical Work in the Troops”, etc.

The name of this remarkable man, a scientist, surgeon, patriot, and warrior, was given to the Neurosurgical Institute of the Russian Academy of Sciences, Clinic of the Surgery Department of the Sechenov First Moscow State Medical University, and Chief Army Hospital in Moscow. The entire many-sided activity of N.N. Burdenko is a brilliant example of a harmonious combination of the theory and practice, which was driven by the urgent needs of the country’s health care system.

Vladimir Nikolaevich Shamov (1882—1962), an outstanding national neurosurgeon and transfusiologist, great administrator and clinician, Academician of the Academy of Medical Sciences of the USSR, honored scientist of Russia, laureate of the Lenin Prize, and major-general of the medical service, was one of the closest comrades of Burdenko and his deputy during the Great Patriotic War. From the first to last days of the war, he was the Red Army chief surgeon deputy. In this senior and responsible position, his talent of an organizer of surgical care to the wounded got flourished. Being in the field army, V.N. Shamov directly managed the work of army and field surgeons, took part in numerous front conferences of surgeons, and actively participated in preparation of instructions, directions, and guidelines that regulated the activities of army surgeons in the sphere of surgical care to wounded warriors.

During the war, V.N. Shamov focused on the development of an edifice system of neurosurgical care in the field army and on immaculate administration of the blood transfusion service. The principles of management of cerebral gunshot injuries described in his many works laid the foundations of the instructions for treating cerebral injuries during the Great Patriotic War. He actively organized specialized medical care to head wounded warriors during the war. The following works belonging to this area should be mentioned: “Management of Medical Care to Patients with Gunshot Skull and Brain Wounds”, “Certain Principles of Treating Infected Brain Wounds”, “Basic Principles of Treating Gunshot Brain Wounds”, and “Management of Neurological Care during the Great Patriotic War”. In the multivolume edition “The Experience
of Soviet Medicine in the Great Patriotic War, 1941—1945”, the fourth and the fifth volumes (“Gunshot Wounds and Injuries of the Skull and Brain” and “Course and Outcomes of Gunshot Head Wounds Depending on Different Conditions of Army Combat Operations”) were written under his supervision and were edited by himself.

N.N. Burdenko highly appreciated work of his deputy: “A major-general of the medical service and Honored Master of Science of RSFSR V.N. Shamov is one of the most outstanding surgeons of our country and is one of the initiators and founders of the scientific development of the blood transfusion issues. A great scholar and initiative and courageous surgeon with marvelous skills and a broad range of the surgical activity, V.N. Shamov conducts extensive research on provision of surgical care to the wounded”.

The institution of chief front surgeons facilitated lucid succession and consistency in work of medical institutions of the surgical profile and rational organization of surgical care in the war years. Outstanding and famous surgeons of our country, including M.N. Akhutin, A.N. Bakulev, A.A. Vishnevskiy, N.N. Elanskiy, I.S. Kolesnikov, I.A. Krivorotov, P.A. Kupriyanov, P.N. Napalkov, V.I. Popov, and many others, occupied these positions of high responsibility and complexity during the war. Among chief front surgeons, Alexander Ivanovich Arutyunov (1904—1975), an outstanding Soviet neurosurgeon, great organizer of health care and brilliant clinician, head of a large school of neurosurgeons, Academician of the Academy of Medical Sciences of the USSR, Honored Master of Science of the Ukrainian Soviet Socialist Republic, and colonel of the medical service holds pride of place.

The Arutyunov’s significant contribution to the theory and practice of field neurosurgery, his talent of a scientist, organizer, and surgeon manifested themselves especially brightly in the years of the war, when he held positions of the army surgeon in the 6th and 9th armies of the Southern Front, chief surgeon of the North-Caucasian Front (1941—1943), South-Western Front and Third Ukrainian Front (1943—1944), and consulting surgeon of the Chief Sanitary Department of the Red Army (1944—1945) at the final stage of the war. In those years, he applied the maximum forces and skills to solve the main task of establishing a well-balanced system in working of field medical evacuation services and front surgical services. One of the certification documents of the chief surgeon of the Third Ukrainian Front A.I. Arutyunov, which is available in the archives, says: “A highly qualified field surgeon and great organizer, he carried out large and fruitful work to manage surgical care and treatment of wounded warriors during the last combat operations. Due to the tireless activity of comrade Arutyunov, surgical care was significantly improved during the past combat operation. Coming to the battlefield and army areas, he did his best to ensure complete surgical care of the wounded. The well-organized surgical work decreased the complication and mortality rates among wounded warriors in the army and battle-field areas. He is fully qualified for his position”.

Alexander Ivanovich made an essential contribution to the solution of field neurosurgery issues. His studies, which were devoted to these issues, provided the basic principles of neurosurgical care at different stages of medical evacuation and developed methods of treating suppurrative intracranial complications. During the war, he published the following papers: “On Closed Cerebral Injury”, “Secondary Bleedings, Their Nosogenesis and Treatment”, “The Results of the First Year of the War in Organization of Surgical Care in the Field, Army, and Front Areas”, “Gunshot Head Wounds”, “Gunshot Wounds of the Great Blood Vessels and Their Treatment at the Evacuation Stages”, etc.

Research and public activities of A.I. Arutyunov complemented each other very well. He was the chairman of the All-Union Scientific Society of Neurosurgeons and the All-Union Task Committee for Nervous System Surgery, first vice-president and then honored president of the Global Federation of Scientific Neurosurgical Societies, etc. More than 80 candidates and doctors of medicine, including 19 professors, were trained under his immediate supervision.

In conclusion, it should be emphasized that medical workers of our country, including a large group of neurosurgeons, served side by side with soldiers and officers of the army and navy throughout the war and fully fulfilled their duty to their country.

Molecular Methods in Diagnosis of Poorly Differentiated Malignant Brain Tumors in Children

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Histological diagnostics of tumors of the central nervous system (CNS) is an important step in the general process of diagnosing and treating cerebral neoplasms that includes, in addition to morphological verification, pre- and post-operative neuroimaging, surgical resection of the tumor, and adjuvant therapy. The correct histological diagnosis allows neurooncologists to choose an appropriate treatment protocol and control the disease. It is known that the use of doxorubicin, an antibiotic exhibiting the anti-cancer activity, for treatment of atypical teratoid/rhabdoid tumor (AT/RT) has improved the overall survival indicators, while glioblastomas (GBs), unlike primitive neuroectodermal tumors of the CNS (CNS PNETs), do not require craniospinal radiotherapy [9, 11, 13, 15, 38, 49, 57].

In the recent years, investigation of the molecular and genetic features of malignant brain tumors in children and development of new diagnostic markers for immunohistochemical analysis have significantly simplified the process of histological verification of tumors; yet, it still requires an attentive attitude and good knowledge of the exact tumor localization [7, 18, 25, 30, 31, 37].

We have analyzed the data collected by the Pathological Anatomy Department of the Neurosurgical Institute of the Russian Academy of Medical Sciences regarding the diagnosis of the three most malignant tumors (CNS PNET, AT/RT, and GB) in children and present the results of the study.

Material and Methods

313 primary intracerebral CNS PNET, AT/RT, and GB cases of the supratentorial (hemispheric and deep) and infratentorial (brainstem) localization in children aged 1 month to 18 years were included into the study. The archival data of the Pathological Anatomy Department for the period from 2000 to 2013 were used. The diagnoses were made on the basis of the criteria suggested by the WHO classification of CNS tumors published in 2000 and 2007 [27, 31, 32].

According to clinical entities, the tumor distribution was as follows: 88 neoplasms were initially diagnosed as WHO Grade IV CNS PNETs; 49 cases were WHO Grade IV AT/RTs; and 176 tumors were WHO Grade IV GBs.

Immunohistochemical analysis was conducted for all the tumors with antibodies for LIN28A (Polyclonal Antibody A177, #3978, Cell Signaling Inc., Boston, MA, USA) at 1:50 dilution and exposure for 30 min at room temperature, but better at 37 °C; for synaptophysin (Monoclonal Mouse Anti-Synaptophysin Clone SY 38 Dako, Denmark); for the glial fibrillary acidic protein (Monoclonal Mouse Anti-Human Glial Fibrillary Acidic Protein Clone 6F2 Dako, Denmark); for the nuclear marker of INI1 gene deletion (Monoclonal Mouse Antibody, Clone MRQ-27, Roche) at 1:250 dilution and exposure for 30 min at room temperature; for the epithelial membrane antigen (EMA) (Monoclonal Mouse Anti-Human Epithelial Membrane Antigen, Clone E29, Dako, Denmark); and for the leucocyte common antigen CD45 (Monoclonal Mouse Anti-Human CD45, Leucocyte Common Antigen, Clones 2B11 + PD7/26, Dako, Denmark).

Assays for the following oncogenes: MYCN (2p24), PDGFRA (4q12), EGFR (7p12), and MYC (8q24.12—q24.13) and the locus 19q13.42 were used for fluorescence in situ hybridization.
Results

88 CNS PNET, 49 AT/RT, and 176 GB specimens were retrospectively revised. Histologically, most GBs were characterized by the classical pattern of malignant astrocytoma with pronounced polymorphism of nuclei and cells, mitoses, proliferation of the vascular endothelium, and necroses with pseudopalisade structures. Tumors with gemistocytes and GBs multiforme were also observed. Pronounced cytoplasmic expression of the glial fibrillary acidic protein GFAP was detected in all GBs.

In the CNS PNET group, based on the morphological pattern characterized by the presence of small-size multilayered rosettes immersed into abundant eosinophilic neuropil (Fig. 1), a subgroup of embryonal tumors with abundant neuropil and true rosettes was defined (the modern name is embryonal tumor with multilayered rosettes (ETMR)); the immunohistochemical analysis of ETMR revealed the expression of LIN28A in multilayered rosettes in all cases. Pronounced diffuse positive expression of LIN28A was also observed in poorly differentiated malignant tumors with true ependymoblastic rosettes and channels resembling the embryonic neural tube, which are the histological structural features of ETMR (Fig. 2). All tumors (except one) with the pronounced cytoplasmic expression of LIN28A also revealed amplification of microDNA at the locus 19q13.42.

According to the morphological pattern, some tumors, which were initially diagnosed as GB, CNS PNET, or AT/RT, were poorly differentiated malignant tumors (PDMTs) and consisted of vast solid areas of small round cells with a high nucleocytoplasmic index, mitoses, thin-walled blood vessels and blood vessels with endothelium proliferation; there were focal necrotic areas with pseudo-palisade structures and/or without pseudo-palisade structures on the periphery of the necrotic tissue (Fig. 3—5).

After the immunohistochemical analysis of PDMTs with the INI1 antibody, the diagnosis of AT/RT was retrospectively made in 57 cases based on the absence of nuclear INI1 expression in the tumor cells, with the expression being preserved in the vascular endothelium (Fig. 6).

Three cases, which were initially diagnosed as CNS PNET, demonstrated pronounced expression of synaptophysin; amplification of the MYCN gene was detected in one tumor. The three above tumors were retrospectively diagnosed as hemispheric neuroblastomas. Later, two of the three tumors relapsed as highly differentiated ganglioneuroblastomas.

The mixed GB/PNET pattern was observed in six cases: there were areas of typical GB and foci of neuroblastic differentiation, forming Homer Wright rosettes (Fig. 4 and 5). The immunohistochemical analysis revealed expression of GFAP in the foci of glial differentiation, whereas the areas of neuroblastic differentiation were immune positive for synaptophysin. One of the six mixed tumors had amplification of the PDGFRA gene, while the pG34R mutation was found in two others (the data provided by Prof. A.G. Korshunov).

To rule out anaplastic ependymoma and lymphoma, the immunohistochemical analysis was performed with the epithelial membrane antigen (EMA) (punctate EMA expression in the tumor cell cytoplasm was detected in three cases (Fig. 7)) and with CD45 (no one case of expression was detected).

All tumors were investigated using fluorescence in situ hybridization to detect possible amplifications of the MYC, MYCN (Fig. 8), EGFR (Fig. 9), and PDGFRA (Fig. 10) genes and amplification of microRNA of the locus 19q13.42 (Fig. 11). Amplifications of the above genes were found to occur more often in GB, in which case we observed both single amplifications and
combinations of amplifications of the MYC (or MYCN), EGFR, and PDGFRA genes, whereas CNS PNETs demonstrated only mutually exclusive amplifications of the MYC or MYCN genes in a smaller number of tumors (Table 1, Fig. 12, 13). No case of amplification of the above genes in AT/RT and ETMR was detected. All the tumors (except one) that were diagnosed as ETMR due to pronounced cytoplasmic expression of LIN28A had amplification of microRNA at the locus 19q13.42.

Then, the total number and percentage ratio of changed diagnoses were calculated (Table 2). Diagnoses proved to be changed most frequently in the group of tumors initially diagnosed as CNS PNET. In this case, diagnoses of ETMR, which (according to the current WHO classification of CNS tumors) also belongs to the CNS PNET group, were not taken into account.

More detailed information about changing the diagnosis by nosologies is shown in Table 3. The diagnoses were changed after retrospective revision of the specimens and immunohistochemical analysis and fluorescence in situ hybridization.

Having compared the histological diagnosis and the clinical data (Table 4, Fig. 14), we found that ETMRs, AT/RTs, and GBs prevail in boys, whereas CNS PNETs occur more often in girls. ETMRs and AT/RTs primarily develop in children under 3 years of age, while children older than 4 years of age more often have GBs. The supratentorial localization is more typical of all the above tumors.

Having investigated 313 most malignant tumors of childhood, we developed an algorithm for diagnosing poorly differentiated malignant tumors occurring in children that is based on detecting the positive expression of LIN28A, synaptophysin, EMA, CD45, and GFAP or the absence of INI1 expression in tumor cells as well as on detection of amplifications of the EGFR and/ or PDGFRA genes (Fig. 15).

In accordance with this algorithm, the diagnosis of CNS PNET should be made only after ruling out the other clinical entities listed above.

**Discussion**

In this paper, we have focused on the retrospective study of the most malignant types of brain tumors in children (CNS PNET, ETMR, AT/RT, and GB), the mean overall survival rate for which does not exceed two years and is 9 months for AT/RT [16], 12 months for ETMR [29], 16 months for CNS PNET [21], and 24 months for GB [26].

The above tumors often have a similar histological pattern of poorly differentiated small round-cell malignant tumor. However, despite the histological similarity, these tumors are absolutely different in their biological properties and approaches to treatment and require individual treatment protocols [5, 6, 8, 12, 14, 19, 20, 24, 50].

In accordance with the current WHO classification of CNS tumors [31], CNS PNET is a heterogeneous group of tumors consisting of non-differentiated or
poorly differentiated cells that are capable of neuronal/neuroblastic, astrocyte, or ependymal differentiation. Tumors exhibiting only neuronal differentiation are called hemispheric neuroblastomas and, in the presence of ganglion cells, hemispheric ganglioneuroblastomas.
In addition to hemispheric neuroblastomas and ganglioneuroblastomas, the current 2007 WHO classification distinguishes among medulloepithelioma, ependymoblastoma, and CNS PNET-NOS, “not otherwise specified”, which is the synonym of supratentorial CNS PNET and is used for non-differentiated or poorly differentiated embryonal brain tumors of any localization in the CNS, excluding the cerebral hemispheres.

All CNS PNETs are malignant tumors with the highest malignancy grade IV; although rare cases of neuroblastoma maturation to more differentiated ganglioneuroblastoma have been reported [2, 10, 40, 56], the prognosis for medulloepithelioma and ependymoblastoma in children under 3 years of age is dismal [31].

In the current WHO classification of CNS tumors, embryonal tumor with abundant neuropil and true rosettes, ETANTR, is listed. First described in 2000 by C. Eberhart et al. [17], this tumor is characterized by the specific morphological pattern, the main feature of which is true ependymoblastic small multilayered rosettes

### Table 1. Identified amplifications of the MYC, MYCN, EGFR, and PDGFRA genes and microRNA at the locus 19q13.42

<table>
<thead>
<tr>
<th>MicroRNA at locus 19q13.42, %</th>
<th>CNS PNET (n=63, ETMR cases are excluded)</th>
<th>ETMR (n=13)</th>
<th>AT/RT (n=57)</th>
<th>GB (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC, %</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>11 (6)</td>
</tr>
<tr>
<td>MYCN, %</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>12 (7)</td>
</tr>
<tr>
<td>EGFR, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15 (8)</td>
</tr>
<tr>
<td>PDGFRA, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21 (12)</td>
</tr>
<tr>
<td>MicroRNA at locus 19q13.42, %</td>
<td>0</td>
<td>12 (92)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amplifications of the above oncogenes and microRNA at the locus 19q13.42 are absent, %</td>
<td>64 (94)</td>
<td>1 (8)</td>
<td>100</td>
<td>117 (67)</td>
</tr>
</tbody>
</table>

### Table 2. Change in the histological diagnosis

<table>
<thead>
<tr>
<th>Clinical entity</th>
<th>Number of cases</th>
<th>Revision of the histological diagnosis and ancillary immunohistochemical test and FISH</th>
<th>Final diagnosis</th>
<th>Change in histological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS PNET</td>
<td>96</td>
<td>88</td>
<td>76</td>
<td>12 (14%) (without ETMR)</td>
</tr>
<tr>
<td>AT/RT</td>
<td>56</td>
<td>49</td>
<td>57</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>GB</td>
<td>197</td>
<td>176</td>
<td>177</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

### Table 3. Change in the histological diagnosis by clinical entities

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>Final diagnosis</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS PNET</td>
<td>ETMR</td>
<td>12</td>
</tr>
<tr>
<td>CNS PNET</td>
<td>AT/RT</td>
<td>8</td>
</tr>
<tr>
<td>CNS PNET</td>
<td>GB</td>
<td>3</td>
</tr>
<tr>
<td>CNS PNET</td>
<td>Anaplastic ependymoma</td>
<td>1</td>
</tr>
<tr>
<td>AT/RT</td>
<td>ETMR</td>
<td>1</td>
</tr>
<tr>
<td>AT/RT</td>
<td>GB</td>
<td>1</td>
</tr>
<tr>
<td>GB</td>
<td>AT/RT</td>
<td>2</td>
</tr>
<tr>
<td>GB</td>
<td>Anaplastic ependymoma</td>
<td>2</td>
</tr>
</tbody>
</table>
throughout the abundant pink neuropil matrix. The tumor may contain solid areas of poorly differentiated cell clusters, channels, and trabecular structures resembling the embryonic neural tube that makes this tumor be very similar to ependymoblastoma and medulloepithelioma, whereas the poorly differentiated areas require differential diagnosis against CNS PNET, AT/RT, and GB. Due to the presence of true multilayered rosettes, W. Paulus и P. Kleihues [41] suggested in 2010 a more correct term “embryonal tumor with multilayered rosettes” (ETMR) to designate this type of tumor. The presence of true multilayered rosettes necessitates a differential diagnosis against tumors whose cells are capable of forming true (not always multilayered) rosettes, including AT/RT, immature teratoma, and anaplastic ependymoma [7, 39]. Another specific feature of ETMR is amplification of microDNA at the locus 19q13.42 [1, 29, 43]. This amplification can be identified by fluorescence in situ hybridization and does not occur in any other tumors with true rosettes, except ETMR [22, 43].

The most convenient and easy-to-use method in routine practice is an immunohistochemical analysis of the tumor with the antibody LIN28A (Cell Signaling Inc.) that enables inerrant differentiation of ETMR from any other tumor due to pronounced expression of LIN28A in the tumor cell cytoplasm [30]. Having observed microRNA amplification at the locus 19q13.42 and pronounced cytoplasmic expression of LIN28A in one case of ependymoblastoma and medulloepithelioma, we came to a conclusion that ependymoblastoma, medulloepithelioma, and embryonal tumor with multilayered rosettes constitute a single clinical entity (unpublished data) and should be singled out in the next WHO classification of CNS tumors to a separate group of CNS PNETs that primarily develop in children under 3 years of age and have an unfavorable prognosis.

Atypical teratoid/rhabdoid tumor rarely presents a classical tumor pattern with the fraction of separately located large rhabdoid cells with the eosinophilic cytoplasm containing globular inclusions and an eccentric nucleus with visible nucleosomes and vesicular chromatin [31]. Often, it is a small round-cell tumor that is histologically indistinguishable from CNS PNET or GB. The patient’s age under 5 years, parabrainstem localization in the perimedullary cistern or cerebellopontine angle as well as neuroimaging data help suspecting AT/RT. Hemorrhage into the tumor [28] and a bandlike wavy rim of enhancement surrounding a cyst or necrotic areas [59] serve MRI signs of AT/RT.

**Table 4. Clinical and morphological characterization of poorly differentiated malignant tumor in children, abs. (%)**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>CNS PNET (n=63)</th>
<th>ETMR (n=13)</th>
<th>AT/RT (n=57)</th>
<th>GB (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (43)</td>
<td>7 (54)</td>
<td>30 (53)</td>
<td>97 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (57)</td>
<td>6 (46)</td>
<td>27 (47)</td>
<td>80 (45)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0—3</td>
<td>23 (37)</td>
<td>12 (92)</td>
<td>46 (81)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>4—11</td>
<td>28 (44)</td>
<td>1 (8)</td>
<td>10 (17)</td>
<td>80 (45)</td>
</tr>
<tr>
<td>12—18</td>
<td>12 (19)</td>
<td>0</td>
<td>1 (1)</td>
<td>85 (48)</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>57 (90)</td>
<td>7 (54)</td>
<td>30 (53)</td>
<td>146 (83)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>6 (10)</td>
<td>6 (46)</td>
<td>27 (47)</td>
<td>30 (17)</td>
</tr>
</tbody>
</table>

**Fig. 14. Clinical and morphological characterization of poorly differentiated malignant tumors in children.**
Before introducing the immunohistochemical analysis of tumors with the INI1 (Clone MRQ-27) or Anti-BAF47 (BD Transduction Laboratories Clone 25/BAF47) antibodies [25, 37] into routine practice, a certain amount of AT/RTs were erroneously diagnosed as CNS PNETs or GBs. Now, it is not difficult to differentiate the above tumors from AT/RT due to the presence of total nuclear expression of INI1 (BAF47) in any supra- or infratentorial tumor, except AT/RT. In this case, the expression of INI1 in the vascular endothelium is regarded as internal control of the INI1 (BAF47) antibody activity, which we use in 1:250 dilution.

To diagnose AT/RT, other antibodies can be used, including vimentin, the epithelial membrane antigen EMA, and smooth muscle actin, which are primarily expressed in large rhabdoid cells. One can also observe expression of glial fibrillary acidic protein and synaptophysin both in the portion of large cells and in small undifferentiated cells [7, 31, 58]. There may be no expression of vimentin, smooth muscle actin, and EMA in the small cell portion of the tumor, which (especially in the case of positive synaptophysin expression) may result in an erroneous diagnosis of CNS PNET; in addition, AT/RTs occur in adults, too [3, 23, 33, 34, 46—48, 53, 54]. Therefore, an immunohistochemical analysis of the tumor with the INI1 (Clone MRQ-27) or Anti-BAF47 (BD Transduction Laboratories Clone 25/BAF47) antibody is the gold standard in establishing the AT/RT diagnosis.

Recently, reports have been published [35, 42, 51, 55] on GBs with PNET-like structure areas characterized by the presence of Homer Wright neuroblastic rosettes. We have also observed these cases when the tumor, along with the classical signs of GB (astrocytoma with pronounced nuclear and cellular atypia, high mitotic activity, vascular endothelium proliferation, and necroses with pseudopalisade structures), contained areas of neuroblast differentiation with positive synaptophysin expression. Although CNS PNET can have astrocyte differentiation by definition [31], these tumors are currently considered to be GBs [42] rather than CNS PNETs with glial differentiation. Attribution of these tumors to GBs is confirmed by the detected aberrations that are pathognomonic for malignant gliomas (amplifications of the PDGFRA gene and mutations of the H3F3A gene — the data provided by Prof. A.G. Korshunov).

Having investigated CNS PNET, ETMR, AT/RT, and GB for the presence of amplifications of the MYC, MYCN, EGFR, and PDGFRA genes and microRNA at the locus 19q13.42, we found that all ETMR cases except one had microRNA amplification at the locus 19q13.42, and pronounced cytoplasmic expression of LIN28A was detected in all cases of ETMR without exception. After comparing the number of

![Diagram](image.png)

**Fig. 15.** The algorithm of diagnosing malignant brain tumors of supra- and infratentorial localization in children.
detected amplifications of the MYC, MYCN, EGFR, and PDGFRA genes, we found that the GB genotype has the highest rate (33%) of cytogenetic abnormalities, and the number of amplifications of the MYC/MYCN genes in glioblastoma exceeds that in the CNS PNET group where amplifications of the above genes were found in 6% of tumors. The determined amplification rate of the MYC/MYCN genes in CNS PNETs was slightly higher than the figures obtained by S. Miller et al. [36] and S. Pfister et al. [44] who reported amplifications of the MYCN gene in 2 and 5% of cases, respectively. At the same time, they did not detect any amplification of the MYC gene in studied series of 35 and 21 supratentorial CNS PNETs. The highest amplification rate of the MYC/MYCN genes was found by A. Behdad and A. Perry [4] who reported 33 identified amplifications of the MYC/MYCN genes in a series of 24 supratentorial CNS PNETs. In our practice, we have never seen simultaneous amplification of the MYC/MYCN genes in the same tumor. We believe these are two mutually excluding aberrations; or a combination of amplifications of the MYC, EGFR, and PDGFRA genes or the MYCN, EGFR, and PDGFRA genes, which occurs in GB, is possible.

Having investigated 313 newly diagnosed supratentorial (hemispheric and deep) and infratentorial (brainstem) CNS PNETs, ETMRs, AT/RTs and GBs using routine staining with hematoxylin and eosin, immunohistochemical analysis, and fluorescence in situ hybridization in patients aged 1 months to 18 years who were operated on at the Neurosurgical Institute in the period between 2000 and 2013 and having compared the findings with the clinical data, we found that the most common type of malignant neoplasms in children is GB that is a tumor with an unbalanced genetic profile, occurring in 57% of patients. Then, in the descending order of the occurrence rate, tumors were distributed as follows: CNS PNETs were in 20% of patients, AT/RTs were in 19%, and ETMR were in 4%. Among ill children, all the tumor types except CNS PNET were predominantly detected in boys. In addition, all the tumor groups had largely the supratentorial localization. ETMRs and AT/RTs developed in children of the youngest age group; CNS PNETs developed in 81% of children aged 4 months to 11 years, while GBs most commonly developed in older children aged 4 to 18 years.

Retrospectively revising the most malignant types of CNS tumors in children (CNS PNET, ETMR, AT/RT, and GB) and analyzing our experience and challenges we faced in making diagnosis, we developed an algorithm for diagnosis of intracerebral, poorly differentiated malignant tumors in children that is based on the use of immunohistochemical analysis and fluorescence in situ hybridization, which are the simplest diagnostic methods available in most pathological anatomy departments.

According to the algorithm, any small round-cell tumor should be tested using antibodies for INI1, LIN28A, synaptophysin, EMA, the common leukocyte antigen CD45, the glial fibrillary acidic protein GFAP as well as by fluorescence in situ hybridization to detect possible amplifications of the EGFR and/or PDGFRA oncogenes, which enables making the correct diagnosis in the case of AT/RT, ETMR, hemispheric neuroblastoma or ganglioneuroblastoma, anaplastic ependymoma, lymphoma, and GB.

We deliberately did not include the CNS PNET entity (not hemispheric neuroblastoma or ganglioneuroblastoma, but CNS PNET-NOS) into this algorithm, since we believe that the diagnosis of CNS PNET-NOS should be made only after ruling out all the types of poorly differentiated malignant tumors. Currently, the heterogeneous CNS PNET group seems to be the least studied and controversial group of malignant CNS tumors. Molecular studies allowed separating only the ETMR subgroup out of the total CNS PNET group based on microRNA amplification at the locus19q13.41 [36] and expression of the LIN28A protein [45]. Thus, it should be considered reasonable to continue studying the CNS PNET group of tumors, including molecular level research.

Histological diagnosis of CNS tumors requires complete neuromorphologist’s awareness of the patient’s age and exact tumor localization. D. Ellison and S. Love [18] completed the list of clinical data helpful for making diagnosis with the following details: the patient’s gender, family history (including information on hereditary syndromes predisposing to CNS tumor growth), and duration of the clinical signs. In some cases of stereotactic biopsy, brainstem tumors, or certain consistency of the tumor tissue, which allows its easy and safe removal by an ultrasonic aspirator, the tumor fragments sent for histological analysis turn out to be too small, which creates certain difficulties in making the correct histological diagnosis. In practice, we often face not exactly correct expression of certain antibodies: for example, focal synaptophysin expression may be observed in the cytoplasm of GB and ependymoma tumor cells.

Sometimes, every practicing morphologist faces tumors whose histogenesis remains unclear. Identification of these tumors is only possible at the molecular level due to the presence of mutations typical of certain neoplasms [52].

Diagnosis of CNS tumors is a labor-consuming process requiring time, knowledge, and cooperative dialogue of all specialists (neuroradiologist, neurosurgeon, neuromorphologist, and neurooncologist) engaged in the treatment of CNS tumors.

The suggested algorithm and this study answer only a part of the difficult questions faced by the morphologist in everyday practice. Rather, the study is aimed to classify and, to a certain degree, facilitate the diagnosis of malignant tumors in children. It also serves an invitation...
to speculate on the morphological and molecular diagnosis of malignant childhood tumors.

Acknowledgements

The authors cordially thank Prof. A.G. Korshunov for the kindly provided data on the H3F3A gene mutations in glioblastomas and for constructive criticism of this paper. The authors express their special gratitude to workers of the pathological anatomy department of the Neurosurgical Institute of the Russian Academy of Medical Sciences I.V. Shibaeva for the assistance rendered in processing clinical data and I.V. Zubova and T.M. Korshunova for their excellent technical performance of immunohistochemical analysis and fluorescence in situ hybridization.

REFERENCES


**Commentary**

The authors provide a broad review of the recent literature on histological and molecular-biological diagnostics of malignant tumors of the central nervous system in children. Along with known tumors of the central nervous system described in detail in the current WHO classification, the authors pay close attention to diagnosis of primitive neuroectodermal tumors of the CNS (CNS PNETs). The paper focuses on the important role of molecular-genetic analysis in modern morphological diagnosis. Poorly differentiated tumors often have a similar phenotype, and it is possible to attribute the tumor to a certain clinical entity only based on the presence or absence of appropriate genetic aberrations. Currently, a comprehensive approach plays an important role in the tumor morphology. In this regard, the authors propose a diagnostic algorithm for analysis of intracerebral small round-cell malignant tumors of the central nervous system in children that includes routine evaluation of slices stained with hematoxylin and eosin, the use of a wide range of immunohistochemical antibodies, including the LIN28A antibody (CellSignaling Inc.), and molecular-genetic analysis by fluorescence in situ hybridization. Based on the findings of the study, the authors propose to define a new CNS PNET subgroup in the next WHO tumor classification that will include ependymoblastoma, medulloepithelioma, and embryonal tumor with multilayered rosettes as tumors occurring in children under 3 years of age and having an extremely dismal prognosis. The paper deals with topical issues such as a cooperative approach to diagnosis of tumors of the central nervous system, engaging other medical specialists. This study is topical, has evident practical value, and facilitates differential diagnosis of such a poorly investigated group of brain tumors as primitive neuroectodermal tumors in children.

A.P. Ektova (Moscow, Russia)
The Effect of APOE3 Gene Therapy on Structural and Functional Manifestations of Secondary Hippocampal Damages in Experimental Traumatic Brain Injury

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¹A.P. Romodanov State Institute of Neurosurgery, Kiev, Ukraine; ²D.F. Chebotarev State Institute of Gerontology, Kiev, Ukraine

Aim of the study was to investigate the efficacy of gene therapy for traumatic brain injury (TBI) by evaluating the effect of liposomal transfection of the brain tissue with an APOE3-containing plasmid vector on the structural and functional manifestations of secondary brain injuries in acute experimental TBI in rats of various ages. Material and methods. Severe diffuse TBI was inflicted in rats under general anesthesia by weight (450 g) dropped from a height of 1.5 m. A suspension of DOTAP liposomes bearing 25 µg of a plasmid vector pCMV-SPORT6 with cDNA of the APOE3 gene was infused intraventricularly using ALZET osmotic pumps. After investigation of motor functions (using a composite neurological motor score) and cognitive functions (Morris water maze), combined morphological, electron microscopic, immunohistochemical, and morphometric studies of the CA1 hippocampal field were conducted in rats on days 5 and 10 after TBI and gene therapy. Results. Significant changes in the morphofunctional state of the hippocampus as well as in the neurological and cognitive functions were observed in a model of severe TBI in adult and old Wistar rats. Gene therapy, specifically cationic liposome-mediated transfection of central nervous system cells with the plasmid vector carrying the human APOE3 gene, decreased TBI-induced death of neurons and improved a qualitative composition of the neuronal population, normalized neuron-glia relationships, and decreased gliosis and microglial reaction, axonal damage, myelin destruction, and lipofuscin accumulation. All these effects had age-related peculiarities. A lower intensity of apoptosis processes was observed in the animal brain after gene therapy (the effect was more pronounced in adult animals). These changes were accompanied by faster and more pronounced regression of neurological and cognitive deficits typical of TBI. Administration of the plasmid vector after TBI resulted in a higher survival rate in old animals vs. old animals lacked gene therapy. Conclusion. APOE3 gene therapy has a therapeutic potential in the treatment of severe TBIs.

Keywords: traumatic brain injury, gene therapy, apolipoprotein E, hippocampus, ultrastructure, age peculiarities, neurological impairment, cognitive dysfunction.

Traumatic brain injury (TBI) still remains an urgent social problem; ca. 10 million TBI patients are hospitalized worldwide each year. According to the WHO forecast [1], traumatic brain injury will be ranked third among causes of death by 2020. Another serious problem is the consequences of TBI: in the USA only, 2.5 to 6.5 million people suffer from social and economic challenges associated with neurological, cognitive, and psychosocial effects of TBI [2].

Demographic changes in the modern society and, in particular, the aging of the population, have led to significant changes in the epidemiology of TBI. In the European Union countries, a lower number of severe traffic accidents and a lower mortality from TBI in the young are accompanied by a significantly increased level of brain injuries sustained at home by the elderly. The injury progression in these patients is more severe (e.g., mortality is the highest in patients of over 75 years of age), and the highest number of surgeries for TBIs is performed on patients aged 65—75 [3]. Therefore, it is necessary to study features of TBI progression and treatment in older age groups.

One of the factors underlyng the course of post-traumatic processes in TBI is apolipoprotein E (APOE), a glycoprotein encoded by the APOE gene, that plays a central role in metabolism, transport, and regulation of the cholesterol and triglyceride levels. After TBI, the synthesis of APOE becomes important for repair of the lipid component of membranes of neurons and gliocytes [4, 5]. In addition to the recognized adaptive functions of APOE in injuries to the central nervous system (CNS), the main determinants of the APOE protective properties were recently demonstrated to be its ability to modify the inflammatory response of activated microglia in the brain and protect nerve cells from excitotoxic injury [6, 7].

There are three human APOE alleles: APOE2, APOE3, and APOE4. In contrast to APOE4, carriage of the APOE3 and APOE2 alleles is associated with better structural and functional outcomes in TBI [8, 9]. Therefore, an idea was put forward to use APOE3 and APOE2 proteins as therapeutic agents providing a therapeutic effect. Since APOE does not pass through the blood brain barrier, its synthesis in CNS cells can be amplified by gene therapy (GT), “a therapeutic procedure in which nucleic acids are used to modulate gene functions” [10].

The aim of this study was to investigate the efficacy of gene therapy for TBI by evaluating the effect of liposomal transfection of the brain tissue with an APOE3-containing plasmid vector on the structural and functional manifestations of secondary brain injuries in acute experimental TBI in rats of various ages.

Materials and Methods

The study was conducted in 25 adult (6—8 months) and 20 old (24 months) Wistar male rats. Changes in the cognitive function, exploratory behavior, and emotional state were evaluated at various times after TBI and
introduction of a plasmid vector (Pl). For morphological studies of the hippocampus and assessment of brain cell apoptosis, the animals were sacrificed on days 5 and 10 after TBI and/or introduction of the vector. The animals were divided into ten groups:

— two control groups: one group of 5 intact adult rats and the other of 4 old rats;
— four TBI groups: two groups of adults rats (5 each) and two groups of old rats (4 each) with experimental TBI;
— four TBI + Pl groups: two groups of adults rats (5 each) and two groups of old rats (4 each) with experimental TBI and a cannula placed in the left lateral cerebral ventricle and connected to an ALZET osmotic pump (DURECT Corp, USA) implanted under the dorsal skin, which infused cationic liposomes and the APOE3-carrying plasmid vector for 25 h at the rate of 1 µL/h (1 µg of the vector per hour).

Severe diffuse TBI was inflicted in rats under general anesthesia by weight (450 g), dropped from a height of 1.5 m [11]. Simulation of experimental TBI and subsequent surgical procedures associated with cannula placement and administration of appropriate solutions were performed under general anesthesia (0.7 mg/kg ketamine, intramuscularly). A suspension of DOTAP Methosulfate cationic liposomes (Sigma, USA) containing 25 µg of a pCMV•SPORT6 plasmid vector (Invitrogen, USA) with the human APOE3 gene under the control of cytomegalovirus promoter was used as a therapeutic agent.

The animals were sacrificed by intraperitoneal injection of a thiopental sodium solution (200 mg/kg). The transfection efficiency (presence of APOE3-mRNA) was confirmed in the cerebellum and medulla oblongata by visualization of amplification products (295 base pairs (bp) and 180 bp for the first and second pairs of used primers, respectively) using a reverse transcription polymerase chain reaction (RT-PCR).

**Morphological examination.** The brain (a portion from the chiasm to the midbrain) was fixed in a 4% paraformaldehyde solution in 0.1 M phosphate buffer for 20 h. The right part of the brain was separated for further processing and confocal microscopy studies. Another part was dehydrated and embedded in paraffin (paraplast) by a standard procedure. Frontal serial sections (6 µm thick) were excised from the hippocampus and used a FV1000-BX61WI confocal microscope (Olympus, Japan) available at the center for shared usage of the Bogomolets Institute of Physiology.

**Electron microscopic study.** Frontal plane slices (0.5 mm thick) were excised from the hippocampus during the sacrifice and were processed according to the standard procedure of sample preparation for electron microscopy. Semithin sections (1 µm) of the hippocampus were stained with toluidine blue and used to localize the CA1 hippocampal field, from which ultra-thin sections (60—70 nm) were prepared for examination on a PEM125K electron microscope (Selmi, Ukraine).

Semithin sections were also used for morphometry, determination of a linear density of neurons (LDN), glia (astro- and oligodendrocytes) (LDG), and microglia (LDM) of the CA1 hippocampal region (100 fields per group using a ×20 objective and a ×10 eyepiece), i.e. counting of the number of cells per unit of the hippocampus length.

The fraction of destructively changed mitochondria (MTs) in the cytoplasm was determined by counting the total number of MTs on a microphotograph and calculating the percentage of destructively changed ones. To determine the volume fraction of lipofuscin (Lf) in the neuron cytoplasm, the Lf total area was measured, and the volume fraction (percentage) was calculated as the Lf to cytoplasm area ratio. The fraction of damaged myelin fibers in the neuropil was calculated by the following formula:

\[(\text{number of damaged axons/total number of axons}) \times 100\%\]
Motor function analysis [12]. A 5-point scale (from 0 — severe injury to 4 — normal motor function) was used to assess a set of indicators on the day of the experiment beginning before inflicting injury and on days 1—7 after the injury. The indicators were as follows:

1) left forelimb flexion during suspension by the tail;
2) right forelimb flexion during suspension by the tail;
3) left hindlimb flexion with the forelimbs remaining on a flat surface while the hindlimbs suspended by the tail;
4) right hindlimb flexion with the forelimbs remaining on a flat surface while the hindlimbs suspended by the tail;
5) resistance to lateral push to the left;
6) resistance to lateral push to the right;
7) ability to stand on an inclined plane in the left direction;
8) ability to stand on an inclined plane in the right direction;
9) ability to stand on an inclined plane in the vertical direction.

The three latter tests assessed the ability of an animal to stand on an inclined plane at an angle of 40° (the maximum score of 4), 37.5° (3), 35° (2), 32.5° (1), and less than 32.5° (0). The composite neurological motor score for each animal was calculated by totaling of individual test scores.

Analysis of cognitive functions. Evaluation of animal spatial memory in the Morris water maze was performed on days 7—10 after injury [13]. A total of 16 trials (4 per day) were conducted, in which rats learned how to find a platform hidden under the surface of colored water, relying on external visual references. Each day during the study, the “searching time” indicator was determined for each rat as a mean time of 4 trials (in seconds) required for the animal to reach the platform. The mean searching time for each group in the experiment was calculated based on these data for a specific day of the study. Longer searching time was indicative of more pronounced deficit in spatial memory and learning ability.

Statistical analysis was performed using the nonparametric Wilcoxon-Mann-Whitney test.

Results and Discussion

Light-optical histological examination on day 10 after injury revealed pronounced structural changes in neurons, glial cells, and capillaries of the brain. They were characterized by fragmentary detachment of the leptomeninges, their swelling, and dissection by diffuse-focal (often massive) agglomerations of modified erythrocytes, the formation of zones with necrobiotically changed nerve cells around hemorrhages, and diffuse edema of cerebral tissue. Areas of neuron loss, i.e. a neuronal depopulation in the hippocampus, were detected in the CA1 hippocampal field. LDN was significantly reduced (1.4-fold) in TBI (Fig. 1).

Several, most common types of neurons of the CA1 field were distinguished: unchanged large (hypertrophic) and hyperchromic. An increase in the number of hyperchromic neurons, with the number of unchanged neurons being reduced, was the most striking finding. The results of an electron microscopic analysis indicate significant destructive changes in the CA1 hippocampal field in TBI and an increase in TBI heterogeneity. Both apoptotically changed, dying cells and activated cells were observed among hyperchromic neurons (Fig. 2). Intranuclear inclusions, of fibrillary kind usually, were often present in neuronal nuclei (Fig. 3), which may indicate profound rearrangement of nuclear proteins and the start of irreversible destructive processes in the nucleus. Vacuolation of Golgi cisterns and significant changes in MTs were observed in the neuronal cytoplasm. Most MTs were represented by destructively changed and dramatically swollen vacuolated forms with destruction and dyscomplexation of chistae and damaged membranes (see Fig. 3). Mitochondrial membrane remnants were incorporated into residual Lf bodies and granules, the volume and amount of which increased from 1—4 in control groups to 10 or more in TBI groups (see Fig. 3).

Application of gene therapy (TBI + Pl) was associated with the fact that the TBI-induced destructive and degenerative changes in neurons were less intense and extensive. Induction of the APOE3 synthesis had a positive effect on the state of nervous tissue and prevented the development of secondary disintegretion zones in the injured brain. The fraction of destructively changed MTs in neurons was lower than that in the TBI group: 55 and 70%, respectively (see Fig. 3). GT not only reduced the level of MT destruction but also altered the ratio of functionally different organelles. In the TBI + Pl group, the fraction of unchanged and functionally active (moderately swollen) organelles was slightly increased due to a reduction in the amount of destructive forms (dramatically swollen at the initial stages of membrane destruction). GT had a much more pronounced effect on Lf accumulation in younger animals compared to older ones. For example, the fraction of Lf in the cytoplasm of old rats decreased due to treatment from 12% of the area in the TBI group to 11% in the TBI + Pl group. In this case, the inhibitory effect of GT on accumulation of Lf was stronger in adult rats: the Lf fraction amounted to 5% of the cytoplasm area in the TBI + Pl group and to 8% in the TBI group (see Fig. 3).

After TBI, deep ultrastructural changes were detected not only in the perikaryons but also in the processes of nerve cells. More than 1/3 of myelin fibers appeared to be damaged (Fig. 4). A rather typical reaction is damage of axons in the form of their local swelling and deformation of the axial cylinder, its obliteration, and, in some cases, detachment from the myelin sheath (with the formation
of vacuoles between them) that was combined with disintegration, homogenization, and destruction of intracellular neurite structures. There were marked changes in the cytoskeleton, such as damage to a neurofilament and local (less often, complete) loss of microtubules, which led to disruption of axonal transport.

Significant changes occurred in axonal MTs: dyscomplexation of cristae and dramatic swelling, associated with hypertrophy of some organelles, were observed. There was disruption of myelin sheaths in the form of their dissection, disaggregation, disruption of the lamellar structure, and formation of swellings and protrusions. In addition, there were destructive changes in the synapses. Local damages to the axolemma cause the release of calcium, which leads to intraxononal disruption of the cytoskeleton and MTs as well as interneuronal connections. Damage to MTs may also lead to the release of cytochrome C that, in turn, activates catalases and plays a certain role in neuronal apoptosis. TBI-induced destructive and degenerative changes in axons were less intense and extensive in the case of gene therapy (TBI + Pl). In particular, the axonal structure was less damaged in the TBI + Pl group than in the TBI group. Both the structure of the axial cylinder, its cytoskeleton, and MTs and the structure of myelin sheaths were normalized. Swelling and deformation of axons were less common. The fraction of damaged myelin fibers in the TBI + Pl group was 22%, whereas it amounted up to 35% in the TBI group.

Immunohistochemical analysis of apoptosis. The structure of hippocampal pyramidal layer is affected by TBI; there appear areas of local thinning with the loss of neurons (due to their destruction and elimination). GT prevented death of some neurons in the injured brain, and LDN of the hippocampus was 12% higher in the TBI + Pl group than in the TBI group. Also, the qualitative composition of the neuronal population was improved: an increase in the number of hyperchromic neurons was less pronounced, which was more evident in old rats. The observed decrease in the number of neurons in TBI is closely related to the apoptotic processes that, most likely, occur within the first days after injury [14]. The TUNEL assay showed that on day 10, and even on day 5, after injury, the level of apoptosis was low in all studied groups: the number of cells in the apoptotic state was less than 4.4% of the total cell number (Fig. 6).

The severity of apoptotic processes in the brain significantly increased with age. In all experimental groups, AI of intact old rats was 5—6 times higher than that of adult rats (see Fig. 6). The maximum level of apoptotic death of neurons and glia was observed after injury (in the TBI group), which was particularly evident in old animals. The difference with the intact control, however, was more pronounced in adult rats: their AI increased 6 times, on average, whereas only a 2.6-fold increase was in old animals.

After TBI, the apoptotic processes in all experimental groups were more intense after 5 days than after 10 days, indicating gradual attenuation of the apoptotic activity. However, the differences between AI values on days 5 and 10 were statistically significant only in adult animals from TBI and TBI + Pl groups, which, in our opinion, reflects a better ability of adult animals to restore nerve tissue and block apoptosis compared to old animals. In the TBI group, AI increased more in adult rats than in old ones.

Application of GT (TBI + Pl) induced positive dynamics of cell death: there was a decrease in AI on days 5 and 10 after injury compared with the TBI group. GT was more effective in the group of adult animals.
Compared with the TBI group, administration of the plasmid vector resulted in a 1.25-fold decrease in AI on day 5 and a 1.20-fold decrease on day 10. At the same time, in old animals, there was only a 1.13-fold decrease on day 5 and a 1.09-fold decrease on day 10. The less pronounced effect in old rats may be attributed to pre-existing age-related morphological changes of nerve tissue. A high variability of AI values in these groups prevents any conclusions on the validity of the decrease due to gene therapy. However, given the data on LDN, which was 1.17 times higher in the TBI + Pl group than in the TBI group, as well as improved indicators of some structural characteristics of the nervous tissue, it is possible to claim that GT has an inhibitory effect on the apoptotic processes and a positive influence on the morphofunctional condition of neurons in the CA1 hippocampal field.

A characteristic feature of the TBI-induced changes in the hippocampus is pronounced gliosis. It was less intense in the TBI + Pl group.

A morphometric analysis of macroglia revealed a significant increase in LDG (total of astro- and oligodendrocytes) (Fig. 7). The highest increase in LDG was observed in the TBI group (41%), whereas it was less pronounced (8%) in the GT (TBI + Pl) group.

According to electron microscopy, rats from the TBI group had marked degenerative changes in their glia, such as significant accumulation of Lf (1—4 granules in the cytoplasm of control animals vs. 10 or more in the TBI group) and vacuolation of the Golgi cisterns. The number of Lf granules in gliacytes increased to a greater extent than in neurons, and the granule volume increased as well. There was also an increase in the number and size of residual bodies. An important component of post-TBI changes in the nervous tissue is a redistribution of intra- and intercellular fluid, which is manifested as swelling of astrocyte processes (especially pronounced in perivasal areas and, in some cases, quite large-scale), focal or diffuse swelling of bodies of gliacytes and neurons and neuronal processes.
TBI-induced destructive and degenerative changes in gliocytes were less intense and extensive in the case of GT (TBI + Pl). The morphometric analysis showed that GT contributed to smaller accumulation of Lf in gliocytes; compared to the control group, the number of Lf granules was 3 and 6 times higher in TBI + Pl and TBI groups, respectively. However, swelling remained significant, especially in the area of astrocyte processes in the pericapillary zone.

Hyperplasia and hypertrophy of the microglia also occurred in TBI. At the ultrastructural level, there were large macrophage-like cells with numerous large electron-dense vesicles. The morphometric analysis of LDM revealed signs of its activation in the hippocampus of injured animals. A significant increase of LDM in all experimental groups compared to control animals reflects proliferation of microglia and migration of its cells to a lesion. The increase in LDM was much stronger than that in LDG (in 4.5 times) (see Fig. 7). The GT (TBI + Pl) group had a tendency to inhibit the increase in LDM.

Immunohistochemical analysis of neurons and astrocytes (double immunolabeling). A typical sign of hippocampal damage in severe diffuse experimental TBI was activation of neuron-glia relationships. The data of fluorescent immunohistochemical confocal microscopy confirmed the loss of neurons (lower density of NeuN-positive neurons) in the hippocampus. The observed changes included hypertrophy of astrocyte bodies, an increase in their volume, and an increase in the number and size of their processes whose branching was increased, and the branching pattern changed from star-like to bushy (Fig. 8). In this case, astrocyte bodies got closer to the neuron layer; the contact area of neurons and astrocytes was enlarged, and astrocyte processes often spread in neurons of the pyramidal layer. GT had a positive influence on the structure and ultrastructure of the hippocampus, including a reduction in the number of astrocytes in the radial layer and normalization of their structure (process branching in the TBI + Pl group was predominantly star-like, as in the control).

The identified distortion of the CA1 hippocampal field cytoarchitectonics is the morphological substrate of cognitive impairments in traumatic brain injuries.

Motor function analysis. Since a significant part of old animals died after TBI, and the state of survivors was...
often unsatisfactory, they were not included in functional studies whose results are presented below. However, administration of the plasmid vector after TBI (TBI + Pl group) increased the number of animals survived till day 10 (the day of sacrifice).

Investigation of neurological disorders in rats with experimental TBI using the composite neurological motor score (Fig. 9) revealed that animals subjected to liposomal transfection of brain tissue with the APOE3-carrying plasmid vector demonstrated in the posttraumatic period faster regression of neurological symptoms compared with rats in the TBI group and rapid recovery of impaired functions, including the strength and range of reflex forelimb and hindlimb movements and motion coordination. On days 3 and 4 after injury, the composite neurological motor score in treated animals was significantly higher than that in the group of rats with TBI: (24.0±3.81) points on day 3 after injury compared to (17±2.95) points in the TBI group (p=0.02); (26.4±3.36) points on day 4 after injury compared to (19.8±3.27) points in the TBI group (p=0.02).

**Cognitive function analysis.** The evaluation of the gene therapy impact on the dynamics of spatial memory deficits in rats with TBI revealed that the searching time required for control animals to reach a platform rapidly decreased during the posttraumatic period (Fig. 10). In the TBI group, the searching time decreased at a slower rate and statistically significantly exceeded this indicator for the control group throughout the study: (74.2±4.32) s vs. (17.2±3.27) s on day 8 (p=0.01); (64.2±4.21) s vs. (16.2±2.49) s on day 9 (p=0.01); (61.2±4.32) s vs. (9.6±2.41) s on day 10 after injury (p=0.01). In the TBI + Pl group, APOE3 gene transfer facilitated a more rapid regression of cognitive disorders, in particular, a reduction in deficit of spatial memory and learning ability. On day 8 of the experiment, the searching time value in the experimental group was (49.0±6.21) s compared to (74.2±4.32) s in the TBI group (p=0.01); on day 9, it was (34.8±3.96) s compared to (64.2±4.21) s (p=0.01); and on day 10, it was (30.2±3.96) s compared with (61.2±4.32) s (p=0.01).

In the recent decades, advances in molecular biology and genetics made it possible to use new approaches to evaluation of dynamics of structural and functional changes in TBI. It has been recognized that pathological changes in traumatic brain injury are “not isolated events but processes set in motion by mechanical impact. These processes are not completed within any reasonable period of time after injury” [15]. At present, primary brain injuries are proved to develop within a relatively short period of time. They are followed by a process referred to as “delayed cell death”. In this case, the number of nerve cells dying due to secondary injuries may greatly exceed that due to primary injury. With allowance for this, the contribution of delayed cell death to the development of neurological deficit appears to be very significant, and the length of the period of secondary death of nerve cells defines the so-called “therapeutic window” that enables therapeutic measures facilitating neuroprotection [16, 17].

**Conclusions**

The study results demonstrate that severe diffuse experimental TBI is characterized by the development of secondary injuries to the hippocampus with disruption of its cytoarchiteconics as well as by the development of destructive and degenerative changes in all of its elements (neurons, glia, capillaries). These structural-cellular disruptions manifested at the functional level as neurological deficit and cognitive impairments. The use of gene therapy (liposomal transfection with the APOE3-carrying plasmid vector) had a positive effect on the structure and ultrastructure of the hippocampus. TBI-induced death of neurons was decreased (the decrease was more pronounced in adult animals than in old ones);...
Fig. 8. Immunofluorescence (laser scanning confocal microscope) of NeuN-positive neurons (green) and GFAP-positive astrocytes (red) of the hippocampal CA1 field of rats.

TBI group: hypertrophy of astrocyte cell bodies, increased number of their processes, changes in the process branching pattern from star-like to bushy; TBI + Pl group: normalization of processes branching forms with preservation of hypertrophy (*200 for the control group and TBI, and *400 for TBI + Pl).

The qualitative composition of neurons was improved; also, there was a reduction in axonal damage and myelin destruction, gliosis and microglial reaction, pericapillary edema and lipofuscin accumulation; the structure of astrocytes was normalized, and the number of small neurons in the hippocampal radial zone was increased. These changes were accompanied by lower severity and more faster regression of neurological and cognitive deficits caused by injury.
**Fig. 9.** The effect of gene therapy on the dynamics of neurological deficit in adult rats with experimental TBI.

Here and in Fig. 10: * — $p<0.05$ compared to the control group, # — $p<0.05$ compared to TBI.

**Fig. 10.** The effect of gene therapy on the dynamics of cognitive deficit in adult rats with experimental TBI.
The literature data [4, 6, 7, 18, 19] suggest several possible mechanisms of APOE influence on TBI outcomes, namely: 1) the influence of APOE on normalization of the lipid component of nerve cells; 2) a role of APOE in the regulation of glial reactions and inflammatory response of the CNS to injury; 3) antioxidative effects of APOE; 4) involvement of APOE in the regulation of cell death; 5) the effect of APOE on expression of other genes and regulation of genomic response of CNS cells in the case of CNS diseases and injuries.

In recent years, interest in APOE neuroprotective properties has led to the development of another approach to its use in experimental traumatic and ischemic brain damages. In contrast to the full APOE molecule, peptides corresponding to an APOE molecule or its functional fragments responsible for binding to low density lipoprotein receptors (this domain is identical in different isoforms of the protein) demonstrated the ability to penetrate through the blood-brain barrier. A team of US scientists from the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry [22] implemented through the interaction of its receptor-binding domains with corresponding LDL-receptors into the injured CNS by gene therapy or another possible way as well as on evaluation of the potential of using APOE or APOE-derived therapeutic agents in clinical practice.

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Commentary

It is now becoming increasingly clear that the course and outcome of traumatic brain injury (TBI) are defined not only by its biomechanism, severity, age, presence of premorbid factors, etc. but also by individual features of the genome of each patient, which refers traumatic brain disease to multifactorial diseases. Over the last few years, genetic studies of multifactorial diseases and traumatic injuries of the nervous system have acquired great importance. The genome defines the presence or absence of genes of predisposition to the development of certain complications and consequences of TBI that, in general, determines the course of traumatic brain disease. The predisposition genes are mutant genes (alleles) coexisting with birth and life; however, under certain adverse conditions (in particular, trauma), they may contribute to the development of a certain multifactorial disease (in particular, traumatic brain disease and its complications) [1].

In particular, one of the factors defining the course of traumatic brain disease was demonstrated to be the presence of a particular allele of the gene encoding apolipoprotein E (APOE), which is involved in the lipid metabolic cycle both in the brain and in the body [2, 3]. The role of the APOE gene was described in detail in a recent review by A.A. Potapov et al. [4].

On the basis of an experimental model of severe traumatic brain injury in adult and old Wistar rats, E.G. Pedachenko and coauthors demonstrated that administration of the APOE3-carrying plasmid vector is associated with significant changes in the morphofunctional state of the hippocampus as well as in neurological and cognitive functions. After analysis of the motor and cognitive functions, a comprehensive morphological, electron microscopic, immunohistochemical, and morphometric analysis of the CA1 hippocampal field was performed on days 5 and 10 after TBI and gene therapy. Animals receiving gene therapy demonstrated faster and more pronounced regression of neurological and cognitive deficits typical of TBI. This was accompanied by a decrease in the intensity of apoptosis (more pronounced in adult animals) in the brain. Introduction of the plasmid vector after TBI significantly increased the survival rate in old rats compared to old animals without gene therapy.

It should be noted that no clear relationship has been established yet between a certain polymorphism and the development of adverse outcomes or complications of TBI. Undoubtedly, further investigation of genetic polymorphism in TBI is crucial for the development of diagnostic algorithms and treatment strategies for traumatic brain disease in order to prevent secondary damage and accelerate recovery of these patients. Therefore, the work of E.G. Pedachenko et al. is topical, interesting to neurologists, neurosurgeons, and specialists in related fields.

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REFERENCES
Glioblastoma Metastases: a Literature Review and a Retrospective Analysis of Six Cases

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Since 1990, cases of glioblastoma (GB) metastases with metastatic foci distant from the primary tumor have been described in the literature. However, the pathogenesis of this process still remains unclear. On the one hand, a metastatic focus is believed to arise due to metatstasizing of the tumor from the primary site; on the other hand, it may occur due to multifocal growth. The article presents a literature review and case reports of patients with GB metastases. Material and Methods. The study included 6 patients (1 female and 5 males) with cerebral GBs who underwent treatment at the Burdenko Neurosurgical Institute (5 patients) and the Department of Neurosurgery of the Research Center of Neurology (1 patient) during 2010—2014. Neurophysiological control was used when the tumor was localized near the eloquent cortical areas and pathways; 4 out of 6 patients were operated on using intraoperative fluorescence diagnosis with a 5-ALA-based agent Alasens. Results. Four patients had metastases within one cerebral hemisphere; in 2 patients, metastases occurred in the contralateral hemisphere within the period ranging from 5 to 18 months after the first surgery. In 2 patients, the primary tumor site was localized near the ventricular system; during the first surgery, the lateral ventricle was opened in 1 out of 6 patients, and the prepontine cistern was opened in another patient. In 2 other operated patients, the primary tumor site was located at a distance from the lateral ventricles, however, the tumor was located near them during recurrence. Metastases of GB were localized near the cerebrospinal fluid (CSF) circulatory pathways in all cases. On the basis of metabolic navigation with 5-ALA, fluorescence of the tumor was observed in 4 patients during both the first surgery (primary tumor resection) and reoperation (metastasis removal). Conclusions. The close relationship between primary glioblastomas and metastases and the CSF circulatory pathways may confirm dissemination of tumor cells with the CSF flow. To our opinion, the close relationship between glioblastomas and the CSF pathways should raise awareness of GB metastasizing. In patients with GBs, metabolic navigation with 5-ALA was effective during both primary surgery and subsequent resection of GB metastases.

Keywords: glioblastoma, metastases, fluorescence diagnosis, 5-ALA.

List of abbreviations:
5-ALA — 5-aminolevulinic acid;
CSF — Cerebrospinal fluid;
CRT — Chemoradiotherapy;
ChT — Chemotherapy;
CT — Computed tomography;
GB — Glioblastoma;
MRI — Magnetic resonance imaging;
PET — Positron-emission tomography;
RS — Radiosurgery;
RT — Radiotherapy;
SBD — Single boost dose;
SRT — Stereotactic radiation therapy;
TBD — Total boost dose;
TMZ — Temozolomide.

Glioblastoma multiforme (GB) or “glioblastoma” is one of the most common tumors of the central nervous system, accounting for more than 62% of all astrocytic tumor cases [1]. Currently, the conventional approach to treatment of most GB cases is combined therapy including surgical intervention and subsequent chemotherapy and radiotherapy (ChT and RT, respectively) [2, 3]. For all types of treatment, the survival rate is less than 10% for GB patients after 5 years [4], and amounts to only 15% after 2 years [5].

Enhanced propensity for relapse and metastasis is a feature of malignant gliomas [6]. Relapses occur in 60—90% of patients and are often localized within 2 cm of the primary neoplasm [7—9]. In 5% of patients, multiple foci may occur after treatment [10] (Table 1). Recurrent tumors developed out of the primary site and genetically similar to the primary tumor tissue are called GB metastases. They can occur both in the same and in both cerebral hemispheres; they can be extracranial and intracranial [1], with the former occurring much rarely [11]. An extracranial metastasis is defined as a recurrent site of GB outside of the brain (e.g., tumorigenesis in the liver, lungs, skin, bones, etc.) [12]. Extracranial metastasis of GB can be accompanied by the transdural spread, particularly, in areas adherent to the skull foramina and sinuses [11, 13]. GB cells can disseminate through the pathway fibers [14—17], CSF system [18], and, less often, hematogenous and contact pathways [7—9]. The brain contains a great number of the associative [18], commissural [14], and projection fibers [17], and the tumor can spread through each of them [19].

The mean survival time for GB relapse is 30 weeks [20]. A surgical approach in this case is determined on the individual basis. A pronounced positive effect of reoperation for recurrent tumors was observed in a number of studies [21—23]. However, the effect in some studies was minor or absent [24—29].

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PROBLEMS OF NEUROSURGERY NAMED AFTER N.N. BURDENKO 2, 2015

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There is no standard approach to the treatment of patients with recurrent malignant gliomas. Systemic ChT, reirradiation, and palliative care are used for treatment in this case. Optionally, radiosurgery (RS) can be used in the case of small tumor foci. Temozolomide (TMZ) and other chemotherapeutic agents are indicated for ChT in patients with recurrent malignant gliomas [30, 31]. Several authors [1, 32] demonstrated the efficacy of fractionated stereotactic radiation therapy (FSRT) in patients with recurrent GBs, with the survival rate amounting to 79% after 6 months and 30% after 1 year.

On the basis of magnetic resonance imaging, positron-emission tomography, or computed tomography (MRI, PET, or CT, respectively), 2 or more isolated GB sites are regarded in the literature either as an initially multicentric tumor [35], or as metastases of the primary tumor site [18, 33, 36, 38], or as two different primary GBs [34].

To differentiate diagnosis between a GB metastasis and a second primary tumor, p53 mutations, PTEN mutations, and p16 deletions [34] as well as a loss of heterozygosity at regions 1p36, 10q15, 19q13, and 22q13, and at the gene regions CDKN2A, PTEN, and DMBT1, TP53 mutations, and EGFR amplification were investigated [36]. These two studies emphasize that the difference in the loci of these mutations enables differentiation between a metastasis of the primary tumor and a second independent GB.

The main mechanism of metastasizing with the formation of an isolated distant metastasis is the spread of tumor cells through the CSF outflow pathways. The predisposing factors include young age, partial resection or biopsy of the tumor as well as opening of the CSF spaces or basal cisterns of the brain [16, 18].

Several researchers suggest using intraoperative fluorescence diagnosis for differentiation of a recurrence connected with the primary tumor site from a GB metastasis [37]. The authors presented a case of 56-year-old patient with a primary GB site in the right occipital region and 3 recurrent foci in the right parietal lobe to demonstrate the capability of intraoperative fluorescence with 5-ALA to detect subependymal tumor spread not visible by MRI.

A number of authors [39—41] note that ChT and RT may cause transformation of tumor cells, their new properties, and increased cell migration; however, this assumption requires further studies. It should be noted that the recurrence-free period after the first surgery varies in a wide range from 3 weeks to several months and even 10 years [42]. In general, the incidence rate of GB metastases within the same hemisphere slightly exceeds the rate of metastases localized in different hemispheres [18, 21, 37].

A study of 30 patients, 8 of whom had GB metastases, demonstrated that the overall survival rate in patients with metastasis was lower than that in patients with a single site of GB. For example, the mean overall survival

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Author</th>
<th>Metastasis location</th>
<th>Supposed tumor genesis</th>
<th>Treatment prior to relapse</th>
<th>Treatment after relapse</th>
<th>Relapse-free period after first surgery</th>
<th>Primary tumor location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aichholzer et al., 2001 [33]</td>
<td>Right basal ganglia</td>
<td>Seeding during stereotactic biopsy</td>
<td>No data</td>
<td>Stereotactic biopsy</td>
<td>3 months and 1 week</td>
<td>Right basal ganglia</td>
</tr>
<tr>
<td>1</td>
<td>Res et al., 2003 [34]</td>
<td>Right frontal lobe</td>
<td>Two primary GBs</td>
<td>Resection</td>
<td>Resection</td>
<td>10 years</td>
<td>Right frontal lobe</td>
</tr>
<tr>
<td>1</td>
<td>Jawahar, 2003 [35]</td>
<td>Left temporal region</td>
<td>Multicentric GB</td>
<td>Gamma Knife</td>
<td>Gamma Knife</td>
<td>3 months</td>
<td>Left frontal lobe (1st patient)</td>
</tr>
<tr>
<td>2</td>
<td>Van Nifterik et al., 2006 [36]</td>
<td>Right frontal lobe (1st patient), Left parietal lobe (2nd patient)</td>
<td>Metastasis of the primary tumor</td>
<td>Subtotal resection, RT in the hypofractionation regimen (42 Gy delivered in 3 Gy), SRT (15 Gy)</td>
<td>Subtotal resection + RT (60 Gy delivered in 30 fractions) + 5 cycles of Temozolomide</td>
<td>16 months</td>
<td>Right frontal region</td>
</tr>
<tr>
<td>2</td>
<td>Jezewski et al., 2011 [18]</td>
<td>Left parietal periventricular region</td>
<td>Metastasis of the primary tumor</td>
<td>Resection + RT (60 Gy delivered in 30 fractions)</td>
<td>Resection + RT (60 Gy delivered in 30 fractions) + Temozolomide + EGFRvIII peptide-based vaccine + Gamma Knife</td>
<td>4—20 months</td>
<td>Left parietal lobe</td>
</tr>
<tr>
<td>7</td>
<td>Cage et al., 2013 [37]</td>
<td>Right parietal lobe</td>
<td>Subependymal and ependymal spread</td>
<td>No data</td>
<td>No data</td>
<td>7 years</td>
<td>Right occipital region</td>
</tr>
</tbody>
</table>
was 27 months in a group of patients with a single GB site and 14 months in a group of patients with GB metastases [6].

Material and Methods

The study included 6 patients (1 female and 5 males) with brain GBs. The patients were treated at the Burdenko Neurosurgical Institute (5 patients) and at the Neurosurgical Department of the Research Center of Neurology (1 patient) during 2010—2014. The median age was 61 years (minimum age: 53 years; maximum age: 66 years). All surgeries were performed using a surgical microscope and microsurgical techniques. Neurophysiological control was used when the tumor was localized near the eloquent cortical areas and conduction pathways; 4 of 6 patients were operated on using intraoperative fluorescence diagnosis with a 5-ALA-based agent Alasens. The fluorescent effect was visualized using a microscope equipped with a fluorescence module. Case reports of patients with GB metastases who were treated at the Burdenko Neurosurgical Institute from 2010 to 2014 are presented below (Table 2).

Results

Four patients had GB metastases within one cerebral hemisphere, and 2 patients had GB metastases in the contralateral hemisphere in a period of 5 to 30 months after the first surgery (Table 2).

A patient with a recurrent tumor in the contralateral cerebellopontine angle (case 5) underwent surgical resection of the primary tumor site in the left temporal lobe (with the patient in the lateral position). Four of 6 patients underwent 2 surgical interventions each to remove a primary tumor site and a tumor metastasis (cases 1—4). In case 6, 3 surgeries were performed, including resection of a primary tumor site and two operations for recurrent GBs. Between surgeries, all the patients underwent CRT according to the standard treatment regimens.

In 2 patients, the primary tumor site was localized near the ventricular system (cases 1 and 2). During the first surgery, the lateral ventricle was opened in 1 patient (case 3), and the prepontine cistern was opened in another patient (case 5), with a patient being in the lateral position. Later, the latter patient was detected with a small size tumor metastasis in the cerebellopontine angle region, on the opposite side; no reoperation was indicated for the patient at the time of writing this article. In 2 patients, the primary tumor site was remote from the lateral ventricles (cases 4 and 6). However, the tumor was localized near the CSF pathways in the case of GB metastasizing (cases 1—6). In case 6, a patient had recurrent GB at the area of the prior surgical site 18 months after the first surgery; the patient underwent reoperation for resection of recurrent GB of the left parietotemporal region without opening the ventricular system. Five months after the second surgery, the patient was again diagnosed with repeated GB relapse localized in the left parietotemporal region close to the posterior horn of the left lateral ventricle. During the third surgery, the ventricular lumen was opened. The patient received combined CRT between surgeries. However, despite the treatment, GB metastases affecting both frontal lobes were detected by control MRI 12 months after the third surgery. Surgical intervention was declined due to multifocal and extensive brain lesion. The patient died from disease progression 35 months after the first surgery.

On the basis of metabolic navigation with 5-ALA, fluorescence of the tumor in 4 patients was detected; MRI detected a lesion in the right parietal lobe with perifocal edema was detected by MRI (Fig. 1a—c).

The tumor in the right parietal parasagittal region was resected using intraoperative neurophysiological monitoring, navigation systems, laser spectroscopy, and fluoroscopic guidance at the Burdenko Neurosurgical Institute on May 10, 2011. The biopsy identified a malignant astrocytic glioma with high cell density and a necrosis area (hematoxylin and eosin staining, ×400). No worsening in the neurological status occurred in the postoperative period. After the first surgery, the patient received 15 courses of Temodal ChT and RT (66 Gy). The patient’s condition remained stable within 1.5 years afterwards. Figure 1 (d—f) shows MRI of the patient 8 months after the first surgery. Slight contrast uptake is observed at the surgery site. MRI performed 18 months after the first surgery revealed GB metastasis at the pole of the right temporal lobe with intense contrast uptake. Methionine PET (Fig. 2) detected a lesion of 32×20×37 mm in size with high metabolic indicators (uptake index of 3.99) in the right temporal lobe.

The patient underwent reoperation for GB metastasis 1.5 years after the first surgery. A glioma of the right temporal lobe was removed using fluorescent assistance and ultrasonic navigation. No worsening of neurological symptoms was observed in the postoperative period. According to the biopsy, the tumor was a malignant gemistocytic astrocytoma with pronounced nuclear polymorphism. Two weeks after the second surgery, the patient underwent radiosurgical treatment.
### Table 2. Clinical data of patients with GB metastases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Gender</th>
<th>Age, years</th>
<th>Primary tumor site location</th>
<th>Metastasis location</th>
<th>Relapse-free period after previous surgery</th>
<th>Treatment prior to metastasis</th>
<th>Primary tumor site location relative to the ventricular system; intraoperative opening of ventricles</th>
<th>Metastasis location relative to the ventricular system and cisterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>62</td>
<td>Right parasagittal parietal region</td>
<td>Right temporal lobe</td>
<td>18 months</td>
<td>2 resections with fluorescence navigation + CRT</td>
<td>Adjoining to the right lateral ventricle</td>
<td>Adjoining to the posterior horn of the right lateral ventricle</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>66</td>
<td>Right frontal lobe</td>
<td>Right temporoparietal region</td>
<td>11 months</td>
<td>2 resections with fluorescence navigation + CRT</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>69</td>
<td>Left frontal lobe</td>
<td>Left parietooccipital region</td>
<td>11 months and 3 weeks</td>
<td>2 resections with fluorescence navigation + SRT using a Primus linear electron accelerator + RS</td>
<td>Opening of the anterior horn of the left lateral ventricle during the first surgery</td>
<td>Opening of the occipital horn of the left lateral ventricle during secondary surgery</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>62</td>
<td>Right frontal lobe</td>
<td>Right temporal lobe</td>
<td>5 months and 2 weeks</td>
<td>2 resections with fluorescence navigation + CRT</td>
<td>No communication with the ventricular system</td>
<td>Near the temporal horn of the right lateral ventricle</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>Left temporal lobe</td>
<td>Right cerebellopontine angle</td>
<td>6 months</td>
<td>1 resection with fluorescence navigation + CRT</td>
<td>Opening of the prepontine cisterns</td>
<td>Cerebellopontine angle region, on the right side</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>Left temporoparietal region</td>
<td>Both frontal lobes in the mediobasal temporal regions</td>
<td>12 months</td>
<td>3 resections + CRT + proton beam therapy</td>
<td>At a distance from the lateral ventricle</td>
<td>Near the occipital horn of the left lateral ventricle (1st relapse). Intraoperative opening of the occipital horn of the left lateral ventricle (2nd relapse)</td>
</tr>
</tbody>
</table>
Fig. 1. MRI of the brain of a female patient with GB in the right parasagittal frontoparietal region (before and after the first surgery). 

a—c — MRI prior to the first surgery; d—f — contrast-enhanced MRI 8 months after removal of GB of the deep portions of the right parietal region. There are no signs of a local relapse.

(gamma knife) of a lesion at the first surgery site in the parietal region on the right side in connection with local contrast uptake in this area. Then, RT (TBD of 54 Gy) to the GB metastasis area at the pole of the right temporal region as well as 12 courses of ChT (Avastin and irinotecan) were performed. The patient died from continued tumor growth in the metastasis area 37 months after the first surgery.

Case Report 2

A 66-year-old male patient was diagnosed with GB metastasis in the right temporoparietal region. Condition: the patient was after resection of GB in the right frontal lobe (April 29, 2013), a course of RT (60 Gy), and 10 courses of Temodal ChTX.

Medical history. The disease began in March 2013 when the patient presented dullness, gait disturbance, general weakness, and tinnitus. MRI of the brain revealed
Fig. 2. MRI and PET before surgery, CT image after surgery, and the data of histological examination of a patient with GB metastasis in the right temporal region. 

a—c — MRI 18 months after the first surgery: signs of GB metastasis; d — PET with methionine 19 months after the first surgery: a focus of increased metabolism at the pole of the right temporal lobe; e — histological picture of a malignant gemistocytic astrocytoma with pronounced nuclear polymorphism. Staining with hematoxylin and eosin (×400); f — CT (on day 1 after the second surgery).

a space-occupying lesion in the right frontal lobe with pronounced perifocal edema and a mass effect (Fig. 3).

29.04.2013, the patient underwent surgery for resection of a tumor of the right frontal lobe using fluorescence navigation, sonography, and neurophysiological monitoring. According to the morphological diagnosis, the growth was a malignant astrocytic tumor with nuclear polymorphism and necrosis. No worsening of the neurological status occurred in the postoperative period. MRI 3 weeks after the surgery detected slight contrast uptake in the periphery of the removed tumor bed. The patient received RT (TBD of 60 Gy) and 7 courses of Temodal ChT. His condition was stable.

The control MRI examination 11 months after the first surgery revealed signs of GB metastasis in the right temporoparietal region (Fig. 4). The patient underwent reoperation on April 28, 2014. GB metastasis in the right temporoparietal region was removed using intraoperative fluorescence navigation. No worsening in the neurological symptoms was observed in the postoperative period. According to the tumor biopsy, the neoplasm was a malignant gemistocytic astrocytoma with pronounced nuclear polymorphism, mitoses, and vascular endothelial proliferation. One month after the second surgery, the ChT regimen was changed to Avastin and irinotecan. Two months after the second surgery, the patient received a course of RT. The tumor bed in the right temporoparietal region was irradiated with the single boost dose (SBD) of 2 Gy up to TBD of 60 Gy based on the 90% isodose according to a 3D-conformal tele-RT technique using a Primus linear electron accelerator (6 MeV, MLC) and with fixation in a mask.

Follow-up MRI 4 months after the second surgery revealed a sign of local relapse in the right parietal region (at the prior metastasis area) in the form of an increased contrast area; no signs of the mass effect were observed. The patient’s condition was stable. ChT with Avastin was
Fig. 3. Preoperative and postoperative MRI scans, intraoperative pictures, and the data of histological examination of a patient with GB of the right frontal lobe.

a—c — MRI before the first surgery: a lesion in the right frontal lobe is visualized.; d — histological picture of a malignant astrocytic tumors with nuclear polymorphism and necrosis. Staining with hematoxylin and eosin (×400); e — a surgical field (the first surgery); f — intraoperative fluorescence in the BL 400 mode (first surgery); g, h, i — MRI 6 months after the first surgery; RT with TBD of 66 Gy; 7 courses of Temodal. Postoperative changes in the primary surgery area are observed.

continued (3—4 courses). Seven months after the second surgery, a second, small size GB metastasis without the mass effect was detected in the splenium region. It required no surgical treatment. Avastin + irinotecan ChT was continued. A total of 12 courses were provided. Currently, the patient’s condition is stable; he continues to receive ChT and is followed-up.

Discussion

The problem of recurrent malignant glial tumors is well known in the literature and arises from a high mitotic activity of the tumor and the ability of tumor cells to migrate and invade the surrounding areas of the brain. Despite the combined treatment of GB patients, the problem of tumor relapse and metastasis unfortunately does exist almost invariably [9, 14, 15, 18, 20].
In 90% of cases, a relapse is detected at the primary tumor site; however, GB metastases may occur in 5% of patients [10]. These metastases arise due to the ability of tumor cells to spread in different ways. In particular, they can disseminate along the fibers of the brain conductive pathways [14, 15, 17, 19] and through the CSF system [16, 18]. The hematogenous and contact pathways of tumor metastasis are much less common [7—9]. In the literature, only single series of GB metastasis observations are reported (see Table 1). In most cases, only single cases are described [23, 26, 33, 37, 40]; 2 cases of GB metastases are described in one study [43], and 8 cases are described in another one [44].

According to the literature [18, 21, 37], GB metastases often occur within the same hemisphere. This fact corresponds to our own data: 4 out of 6 patients had tumor metastases in the ipsilateral hemisphere with respect to the primary tumor site. In our observations, in 2 out of 6 patients, the tumor was located close to the lateral ventricles during the first surgery. The ventricles were opened at the end of surgery in 1 patient. During resection of GB of the medial portions of the temporal lobe in 1 patient (with the patient in the lateral position), the prepontine cisterns were opened. The development of GB metastasis in the cerebellopontine angle on the opposite side was observed. In 2 patients, the primary tumor site was remote from the lateral ventricles, but the tumor was localized near them in the case of a relapse. In case 6 (see Table 2, case 6), a patient underwent 3 surgical interventions. Disease progression in the patient led to 2 sequential GB relapses successfully removed afterwards. It should be noted that the development of relapses was accompanied by a change in their location relative to the primary tumor site towards the occipital horn of the left lateral ventricle. During the third surgery, the lumen of the lateral ventricle was opened. Twelve months afterwards, the patient was detected with GB metastases in both frontal lobes, which caused his death 35 months after the first surgery. Thus, the primary GB tumor site was localized near the CSF pathways (i.e. near the lateral ventricles and prepontine cisterns) in 4 out of 6 patients of our group. This fact indirectly confirms the possibility of tumor spread through the CSF spaces. Later, as the disease progressed, GB metastases occurred in the immediate proximity to either the lateral ventricles or the prepontine cisterns in all cases.

Dissemination of tumor cells through the ventricular system is typical of not only GB. This phenomenon was observed for other central nervous system tumors, in particular, medulloblastomas and ependymomas [45, 46]. For this reason, patients undergo craniospinal irradiation after surgical treatment for preventing drop metastases. GB spreading through the CSF pathways is one of the ways of its dissemination [16, 18]; there are other possible ways of GB spread, in particular, along the major cerebral tracts [7, 9, 14, 15, 17, 19, 21—23, 39].

Because of the infiltrative pattern of tumor growth and the difficulty in defining its limits, various methods of intraoperative navigation were suggested, in particular, fluorescence diagnosis with 5-ALA, which has proved to be effective for both GB and GB relapses [47, 48]. The maximum radicalness of surgery should be achieved with allowance for physiological limits to prevent an increase in neurological deficit in the postoperative period. For this purpose, neurophysiological monitoring is used during surgical interventions in patients with cerebral gliomas [49]. In our study, intraoperative fluorescence navigation with Alasens was used during surgery in 4 out of 6 patients. In this case, intense fluorescence of the tumor was observed during both primary and repeated surgeries. Therefore, in our opinion, fluorescence diagnosis may be effective in both tumor cell detection during primary surgery and relapse of the disease, which has been noted by other authors [47, 48]. According to T.

![Fig. 4. MRI of a patient with GB metastasis in the right parietal region. Axial (a), coronal (b), and sagittal (c) views.](image-url)
fluorescence of the lateral ventricle walls may indicate the subependymal and ependymal spread of the tumor; however, to our opinion [50], weak fluorescence of the lateral ventricle walls is probably related to neurogenesis in the subependymal region and may be detected in the intact ventricle.

Currently, there are no algorithms of intraoperative and postoperative prevention of GB metastases when the primary tumor is located near the CSF circulatory pathways or during intraoperative opening of the latter. These patients should probably be stratified into a group of high risk for GB metastases. Prevention of GB metastases in the brain requires further studies.

REFERENCES


Conclusion

The disease progression in patients with GB significantly more often results in a tumor recurrence. GB metastasizing is much less common and typically occurs within the ipsilateral hemisphere with respect to the primary tumor site. Location of the primary tumor near the CSF circulatory pathways or their intraoperative opening may be the possible mechanisms of GB metastases. Fluorescence diagnosis with 5-ALA is efficient for visualization of both primary GB and its metastases. The problem of GB metastases and prevention of their emergence are understudied now. Further research in this direction is required.

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One of the important problems of neurooncology is recurrence of malignant glial tumors that is associated with high aggression of tumor cells and their capability for invasion and migration. Local and distant recurrences are distinguished; the latter type occurs in about 5% of cases. According to the literature, distant recurrences are often arise within the same hemisphere. The development of these lesions may be related to dissemination of tumor cells via the CSF pathways or to cell migration after CRT.

The authors present a review of the literature and clinical cases, paying attention to the location of the primary tumor site near the CSF circulatory pathways and possible involvement of the pathways in tumor recurrence. The study is illustrated with clinical examples of patients with distant recurrent GBs.

Commentary

The lack of genetic analysis of the biopsy material is a shortcoming of the study. Also, it would be interesting to analyze the tumor tissue samples according to the new molecular classification of GBs and compare the results with the literature data.

The results of the study can be used to increase the treatment efficacy of patients with malignant cerebral gliomas and develop new methods of preventing distant recurrence of malignant gliomas in this type of patients with the possibility of application and implementation in clinical practice. Obviously, the study would be interesting to neurosurgeons, neuroradiologists, chemotherapists, and oncologists.

O. N. Dreval’ (Moscow, Russia)
Quality of Life in Patients with Benign Tumors of the Anterior and Middle Skull Base after Surgery and during Follow-Up


Burdenko Neurosurgical Institute, Moscow, Russia

The outcomes of surgical and combined treatment of 302 patients with benign tumors involving the anterior and middle skull base with allowance for the functional outcomes (immediately after surgery and during the catamnestic follow-up) are reported. The Karnofsky and Rankin scales and the Anterior Skull Base Questionnaire (ASBQ) were used for the analysis. Compared to partial resection, radical tumor resection reduces patients’ quality of life (QOL) in the early postoperative period but improves it subsequently; the use of radiation therapy in the combined treatment for patients with radically incurable tumors does not worsen their QOL in the late postoperative period.

Keywords: quality of life, benign tumors, skull base.

In the early stages of neurosurgery development, mortality rate was considered to be the main criterion for assessing treatment effectiveness in patients with benign tumors of the skull base; it exceeded 50% in the 1930—1950s [1]. Along with the advance in neurosurgery and the decrease in postoperative mortality rates, the degree of surgical radicality associated with the risk of tumor recurrence became the main focus [2]. At that time neurosurgeons started to use the index of patients’ general well-being at various stages of treatment (the Karnofsky index), which had been previously used in general oncology [3]. By the end of the 20th century, a lot of extensive transbasal approaches were suggested to enable maximal surgical radicality; however, they were found to significantly worsen patients’ QOL after surgery [4]. Nonsurgical techniques were developed simultaneously, in particular, radiation therapy enabling tumor growth control with minimal functional consequences [1, 5]. Hence, at the turn of the 21st century, the international neurosurgical community arrived at conclusion that surgical intervention should be aimed at the maximal radical tumor resection without causing subsequent permanent disability of the patient (i.e., the optimal ratio between the surgical radicality and possible functional outcome of surgery needs to be chosen for each particular case) [1].

Assessment of the performance status of patients using the Karnofsky scale is universal and is applied in all areas of neuro-oncology. However, it is difficult to perform proper assessment of patients’ QOL after resection of tumors localized in the anterior and middle regions of the skull base due to possible disorders of the nervous system functions, cosmetic defects, impaired nasal breathing, peripheral hearing loss, as well as chewing, swallowing, and breathing disorders. It is impossible to perform detailed assessment of these disorders using the Karnofsky scale only, which makes it difficult to compare the effectiveness of different surgical methods and radiation therapy.

Few publications have been devoted to studying the functional outcomes of treatment in patients with benign tumors of the anterior and middle skull base. J. Scheitzach et al. [6] reported the outcomes of surgical treatment in 226 patients with skull base meningiomas. In addition to the Karnofsky scale, the authors used the Medical Research Council Neurological Severity Score (MRC-NPS), which has 5 grades of neurological deficit, to assess patients’ well-being. The MRC-NPS scale has a structure similar to that of the Rankin scale that is conventionally used in neurology [7, 8].

These scales are based on assessment of the functional status of a patient by a physician and facilitate statistical analysis of large study groups. However, they are characterized by poor sensitivity, and the most important thing is that they take into account neither patient’s opinion nor significance of the effect of existing disorders on his/her personal life and professional or social activities. In modern medicine, the assessment of patients’ QOL implies obligatory respect to patient’s opinion. A number of questionnaires have been proposed to formalize various aspects of QOL, but no generally accepted questionnaire currently exists. The most commonly used questionnaires for the evaluation of QOL in patients with skull base tumors are the Nottingham Health Profile (NHP), the Innsbruck Health Dimensions Questionnaire for Neurosurgical Patients (IHD-NS), and the Anterior Skull Base Questionnaire (ASBQ). The NHP questionnaire includes a total of 38 questions categorized into domains characterizing energy, pain, emotional reactions, sleep, social isolation, and mobility of a patient. The IHD-NS questionnaire includes a total of 40 questions describing emotional status, communication, physical condition, function of the autonomous (vegetative) nervous system, independence, psychological condition,
and social isolation of a patient. Both questionnaires are composed of only Yes/No questions. I. Mohsenipour et al. [9] showed the correlation between the data obtained using the both tests; the factors affecting patients’ QOL during follow-up after intracranial meningioma resection were identified.

The ASBQ questionnaire, which was widely used by Ziv Gil et al. [10—16] to assess QOL in patients with the anterior skull base tumors, was believed to be optimal for our own needs as well. The questionnaire was originally introduced in 2003; it includes a total of 35 items related to the following distinct domains: role of performance, vitality, physical functioning, social adaptation, impact upon emotions, pain, and specific symptoms. The structure of the questionnaire enables one to thoroughly assess the impact of various factors on the overall QOL, its various aspects, and particular symptoms.

The objective of this study was to identify the factors affecting QOL in patients with benign tumors involving the anterior and middle skull base after surgery and during follow-up, and to optimize the treatment with regard to these data.

Material and Methods

Out of 642 patients operated on for benign tumors of the anterior and middle portions of the skull base at the 6th Neurosurgical Department of the Burdenko Neurosurgical Institute between January 1, 2007 and December 31, 2011, 302 patients completed the ASBQ questionnaire (translated into Russian) 2±1 months and, on average, 36 months (mean time of 39±33—27 months) after surgery.

Out of 302 patients enrolled in the study, 231 were female and 71 were male patients aged 15—80 years (mean age, 51 years). Two hundred and three (67.2%) patients were subjected to surgery only; 99 (32.8%) patients underwent combination treatment (both surgery and radiotherapy). Fifty-nine (20%) patients were previously operated on. Of them, 26 were treated at the Burdenko Neurosurgical Institute and the other 33 patients underwent surgery at other medical institutions.

Based on the clinical and topographic features of the tumor, the study population was divided into three subgroups. In groups 1 and 2, the tumor mainly affected the middle portion of the skull base. Group 1 (n=43) included patients who had a tumor localized in the base of the anterior cranial fossa, in some cases with extracranial spread into the ethmoidal labyrinth and nasal cavity. Group 2 included patients (n=31) with tumors of the base of the middle cranial fossa with median location (i.e. jugum sphenoidale, tuberculum sellae, anterior clinoid processes, and optic foramina); rarely with the intracellar tumor spread into the basilar sinus. Group 3 (n=228) was comprised of patients who had a tumor of more lateral location. This group was thus the largest one and included patients with tumors of the middle cranial fossa and the orbit, spreading to the superior orbital fissure, into the temporal, pterygopalatine, and infratemporal fossae.

The division of patient population into subgroups was based on prevailing tumor location; however, more than one region of the skull base was involved in the tumor process in a number of cases.

Distribution of patients by age is shown in Figure 1. Female patients were significantly predominant in groups 2 and 3, as well as in the total population; the difference was less pronounced in group 1. The age of patients ranged from 15 to 80 years (mean age, 51 years). Most patients were middle-aged and of working age (Fig. 2).

The disease duration between the onset of symptoms and surgery ranged from 1 month to 46 years (mean of 2 years).

Histologically, most tumors were meningiomas (WHO grade I). The histological structure of our material is presented in detail in Table 1.

The compulsory preoperative examination of patients included general examination, conventional clinical and laboratory tests; neurological, neuro-ophtalmological, and otoneurological examination; CT and/or MRI of the brain. The severity of patient’s general well-being was assessed using the Karnofsky scale. The scale has 10 grades, with score 100 corresponding to “no complaints and symptoms of the disease” and 10 being “dying” [3]. The modified Rankin scale was used to measure the degree of dysfunction and disability [17] (Table 2).

The evaluation of the patient’s status using the Karnofsky and Rankin scales and complete neurological examination were also performed at discharge and during follow-up.

A survey, namely the Anterior Skull Base Questionnaire (ASBQ), was used to perform a detailed assessment of the functional status of patients after surgery with regard to their subjective sensations [15]. Testing was performed during 1—3 months after surgery. By that time, the patient’s condition was usually significantly stabilized, postoperative local pain and swelling were reduced, conservative therapy was completed, and the patient returned to his daily life surrounded by relatives. A second testing was completed during the catamnestic follow-up study ranging from 1 to 6 years (mean time, 39 months).

The questionnaire consisted of domains reflecting various aspects of patient’s life.

Each domain included several issues: role of performance (6 items), physical functioning (7 items), vitality/activity (7 items), pain (3 items), impact upon emotions (5 items), and specific symptoms (7 items: smell, taste, sight, etc.) (Table 3). The responses were estimated using scores from 1 to 5, where 1 stood for the negative response and 5 stood for the positive one. For example, the possible answers to the question “How would you define your performance at work?” were as follows: (1) Bad;
(2) Average; (3) Good; (4) Very good; (5) Excellent. In the case of pain assessment, the question “How frequently did you have to take painkillers during the past 4 weeks?” could be answered as follows: (1) Permanently; (2) Often; (3) Quite often; (4) Sometimes; (5) Never. The evaluation was conducted by comparing the average scores in domains and the total average score.

Nonparametric statistical methods (the Mann—Whitney U test) were used for statistical analysis.

**Brief description of surgical interventions**

We studied surgery protocols, as well as preoperative and post-operative data of either CT or contrast-enhanced MRI. Selection of a surgical approach depended mainly upon the topographic features of tumor growth. Hence, the subfrontal approach was frequently used in group 1; the pterional approach was used in group 2; and pterional and/or orbitozygomatic approaches were used in group 3. In most cases, the surgeon tended to perform the maximal possible resection of the tumor; however, when neurovascular structures of the skull base (those lesions could cause patient’s disability or even death) were a part of the tumor, either subtotal or, more rarely, partial resection was performed. Surgery protocols (the surgeon’s opinion), as well as CT and/or contrast-enhanced MRI data, were used for evaluation of surgical radicality. In the absence of contrasted areas on the control scans, the resection was regarded as radical. If more than 70% of a tumor was removed, the resection was regarded as the subtotal one and as the partial one in case of less than 70% of tumor removed. One hundred and seventy (56.3%) patients underwent radical surgery, 119 (39.4%) patients had subtotal resection, 10 (3.3%) patients underwent partial resection, and biopsy was performed in 3 (1%) patients.

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**Fig. 1. Gender distribution of patients.**

**Fig. 2. Age distribution of patients.**

**Table 1.** Distribution of cases with respect to the histological structure of tumors

<table>
<thead>
<tr>
<th>Histology</th>
<th>Tumor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningiomas (79.6%)</td>
<td>WHO grade I</td>
<td>33</td>
<td>26</td>
<td>184</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>WHO grade II</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Nonmeningeal mesenchymal tumors (8.6%)</td>
<td>Juvenile angiofibroma</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hemangioma</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cavernous hemangioma</td>
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<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Solitary fibrous tumor</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td></td>
<td>Cementifying fibroma</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Ossifying fibroma</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Myxoid fibroma</td>
<td>2</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Osteogenic and odontogenic tumors (2.6%)</td>
<td>Osteoma</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Chondroma</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Osteochondroma</td>
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<td>0</td>
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<tr>
<td></td>
<td>Chordoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td></td>
<td>Giant-cell tumor</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Peripheral nerve sheath tumors (5.6%)</td>
<td>Neurofibroma</td>
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<tr>
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<td>Neurinoma</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>10</td>
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<tr>
<td>Undifferentiated neoplastic osseous lesions (1.4%)</td>
<td>Fibrous dysplasia</td>
<td>2</td>
<td>0</td>
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<tr>
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<td>Osteofibrous dysplasia</td>
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<td>0</td>
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<tr>
<td></td>
<td>Aneurysmal bone cyst</td>
<td>1</td>
<td>0</td>
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<td>1</td>
</tr>
<tr>
<td>Cysts (2%)</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Epidermoid cyst</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other (0.4%)</td>
<td></td>
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<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>43</td>
<td>31</td>
<td>228</td>
<td>302</td>
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</table>
Brief description of radiation therapy

If a residual tumor was present, patients were typically subjected to radiation therapy. A total of 99 patients underwent radiation therapy. Of them, 56 patients were subjected to stereotactic radiation therapy (SRT) in the conventional fractionation regimen (about 30 fractions; TBD of 50—60 Gy) and 25 patients underwent SRT in the hypofractionated regimen (3—5 fractions; TBD up to 30 Gy); stereotactic radiosurgery (SRS), namely a single-step delivery of a dose up to 20 Gy, was performed in 5 cases. Twelve patients underwent external beam radiotherapy (EBRT) at the place of residence; proton beam radiation was used in one case.

Results

When analyzing the dynamics of patients’ performance status on the Karnofsky scale, no statistically significant difference in the scores before and after surgery

<table>
<thead>
<tr>
<th>Table 2. The modified Rankin scale [17]</th>
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</thead>
<tbody>
<tr>
<td>No symptoms</td>
</tr>
<tr>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>Moderately severe disability; unable to walk and attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>Death</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 3. Items of the ASBQ questionnaire</th>
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<tbody>
<tr>
<td>Domain</td>
</tr>
<tr>
<td>Role of performance</td>
</tr>
<tr>
<td>1. How would you define your general performance?</td>
</tr>
<tr>
<td>2. How would you define your performance at work?</td>
</tr>
<tr>
<td>3. How would you define your performance at home?</td>
</tr>
<tr>
<td>4. During the past 4 weeks, how much did you participate in social activities?</td>
</tr>
<tr>
<td>5. How would you define your communication with people?</td>
</tr>
<tr>
<td>6. During the past 4 weeks, how much did your health interfere with your performance?</td>
</tr>
<tr>
<td>Physical functioning</td>
</tr>
<tr>
<td>7. How well are you able to walk up the stairs?</td>
</tr>
<tr>
<td>8. How well are you able to lean and stand?</td>
</tr>
<tr>
<td>9. How well are you able to walk 100 meters?</td>
</tr>
<tr>
<td>10. How well are you able to walk 10 meters?</td>
</tr>
<tr>
<td>11. During the past 4 weeks, how much did you stay in bed during the day?</td>
</tr>
<tr>
<td>12. How would you define your ability to carry out routine activities?</td>
</tr>
<tr>
<td>13. During the past 4 weeks, how much did your health affect your activity?</td>
</tr>
<tr>
<td>Vitality</td>
</tr>
<tr>
<td>14. During the past 4 weeks, did you feel physically strong or weak?</td>
</tr>
<tr>
<td>15. During the past 4 weeks, how frequently did you feel tired?</td>
</tr>
<tr>
<td>16. During the past 4 weeks, how much did you accomplish?</td>
</tr>
<tr>
<td>17. During the past 4 weeks, did you feel depressed or happy?</td>
</tr>
<tr>
<td>18. How would you define your motivation to perform various activities?</td>
</tr>
<tr>
<td>19. During the past 4 weeks, how frequently did you feel energetic?</td>
</tr>
<tr>
<td>20. How would you define your relations with your partner?</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>21. During the past 4 weeks, how frequently did you experience pain?</td>
</tr>
<tr>
<td>22. During the past 4 weeks, how frequently did your pain interfere with your ability to perform?</td>
</tr>
<tr>
<td>23. During the past 4 weeks, how frequently did you have to take painkillers?</td>
</tr>
<tr>
<td>Impact upon emotions</td>
</tr>
<tr>
<td>24. During the past 4 weeks, how frequently did you feel tense and nervous?</td>
</tr>
<tr>
<td>25. During the past 4 weeks, how frequently did you have a problem falling asleep?</td>
</tr>
<tr>
<td>26. During the past 4 weeks, how frequently did you feel worried?</td>
</tr>
<tr>
<td>27. During the past 4 weeks, how frequently did you feel relaxed or calm?</td>
</tr>
<tr>
<td>28. How would you define your financial or economic status?</td>
</tr>
<tr>
<td>Specific symptoms</td>
</tr>
<tr>
<td>29. How would you define your appetite?</td>
</tr>
<tr>
<td>30. How would you define your sense of taste?</td>
</tr>
<tr>
<td>31. How would you define your sense of smell?</td>
</tr>
<tr>
<td>32. How would you define your appearance?</td>
</tr>
<tr>
<td>33. How would you define your amounts of nasal secretions?</td>
</tr>
<tr>
<td>34. How would you define your amounts of eye secretions and tears?</td>
</tr>
<tr>
<td>35. How would you define your eyesight?</td>
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</table>
were obtained and the follow-up rates were significantly higher (condition of patients improved) (Fig. 3). Similar outcomes were obtained by assessing functional neurological deficit using the Rankin scale: there was no statistically significant difference after surgery compared to the preoperative scores, but the neurological deficit during follow-up was significantly less pronounced \( (p<0.05 \text{ according to the Mann-Whitney U test}) \) (Fig. 4).

Thus, the results of QOL analysis in the follow-up period coincided with the dynamics of the Karnofsky and Rankin scale scores. It is worth noting, above all, that when comparing the average overall outcomes and the scores within the domains, a significant improvement in QOL in patients during follow-up was revealed compared to the data after surgery (Fig. 5).

No significant difference in QOL of patients older than 60 years was detected compared with the average age group of 30—59 years; in the group of patients younger than 30 years, QOL score was significantly higher both immediately after surgery and during follow-up (Fig. 6).

When comparing the postoperative QOL scores and the follow-up scores, an improvement was observed in all age groups; no significant difference between age groups was revealed.

In patients who had been previously operated on, QOL scores were lower after the second surgery and in the follow-up period (Fig. 7). A more detailed analysis enabled us to specify that statistically significant differences were obtained in the group of patients who had previously undergone surgery at other hospitals. These observations indicated a significant reduction in the QOL score after surgery in the domains “role of performance”, “vitality”, “pain”, “impact upon emotions”, and in the overall score. In the group of surgically naïve patients, statistically higher scores were observed in the domain “specific symptoms”.

There were no significant differences in QOL scores depending on the topographic features of a tumor after surgery and in the follow-up period (Fig. 8).

The dynamics of QOL score depending on the surgical radicality is of interest. For example, the questionnaire completed after surgery revealed that the QOL score in most domains was higher in patients who had undergone partial tumor resection compared to those subjected to subtotal and total resection (Fig. 9a). During follow-up, on the contrary, the best results were reported by the patients who had undergone subtotal and especially total resection, but QOL score of patients after partial tumor resection significantly decreased (see Fig. 9b). Statistically significant differences were obtained in patients who had undergone radical tumor resection: in the domain “specific symptoms” after surgery and in the domains “role of performance”, “physical functioning”, and “pain” in the follow-up period; these patients also reported the best overall QOL score.

The impact of radiation therapy on the QOL of patients in the postoperative period was estimated (com-
Fig. 6. QOL of patients after surgery (a) and in the follow-up period (b) depending on age.

Fig. 7. QOL of patients after surgery (a) and in the follow-up period (b) depending on the presence of surgical treatment in the past medical history.

Fig. 8. QOL of patients after surgery (a) and in the follow-up period (b) depending on the survey group.
Fig. 9. QOL of patients after surgery (a) and in the follow-up period (b) depending on radicality of tumor resection.
Fig. 10. QOL of patients after surgery (a) and during follow-up (b) after surgical and combination treatment.

Fig. 11. Overall QOL score of patients (across the group).

Fig. 12. The dynamics of QOL in patients after surgical (a) and combination (b) treatment.
monly after subtotal tumor resection). No significant differences were found in the overall QOL score of these patients and in the score of most domains after surgery (before radiation therapy) (Fig. 10a) and during follow-up (see Fig. 10b) with the exception of the domain “physical functioning”: in the follow-up period, the score was lower in patients who had undergone the combination treatment.

When assessing results depending on duration of follow-up, it was revealed that there was a statistically significant increase in QOL score between 6 months and 2 years after surgery, followed by stabilization of the scores (Fig. 11).

Meanwhile, the patients who had undergone surgical treatment only showed a tendency towards improved QOL score up to 2—3 years after surgery, and subsequently there was a tendency towards lower scores (Fig. 12a).

It should be noted that patients who had undergone combination treatment had a statistically insignificant decrease in QOL score between 2 and 3 years after surgery, followed by an increase in the late postoperative period (see Fig. 12b).

Discussion

The study of QOL in patients with benign tumors of the anterior and middle portions of the skull base after surgery and during follow-up confirmed some common facts. For example, QOL scores improved between 6 months and 2 years after surgery [13]. However, unlike Z. Gil [13], we did not reveal a decrease in the QOL score in the group of patients older than 60 years compared to the group of 30—59 year-old patients, and the maximal QOL score was detected immediately after surgery and in the follow-up period in patients younger than 30 years; the difference with the older age group was statistically significant. No significant difference was detected when comparing the groups of patients distributed by topographic and anatomical features and by the approaches selected. This finding contradicts the literature data [10, 12, 13] and is most likely to be associated with the fact that our material was comprised only of benign tumors, and no craniofacial en block resection was used for their removal.

Our findings confirmed the decrease in a number of QOL aspects in reoperated patients compared to surgically naïve patients, which coincides with the literature data [13]. However, the decrease was less significant in the patients originally operated on at the Burdenko Neurosurgical Institute compared with the patients originally operated on at other hospitals. This fact justifies the need for standardization of treatment approaches for patients with skull base tumors throughout the country.

Both for the overall QOL score and the scores in domains, a significant improvement in QOL score in patients was observed during the follow-up period compared to the postoperative period. These data coincide with those obtained by assessing patients’ general well-being using the Karnofsky scale and the severity of the neurological deficit using the Rankin scale.

We analyzed the patients’ QOL depending on surgical radicality and obtained some interesting data: if patients who had undergone partial tumor resection “felt better” shortly after surgery, the situation changed radically subsequently. During follow-up, QOL score was significantly higher in patients after subtotal and especially in those after total tumor resection.

We revealed no negative impact of radiation therapy on the overall QOL score and most of the domains studied 3 years or more after surgery; the reduction in these scores during the second year was statistically insignificant. This is inconsistent with the data of other studies [11, 13] that emphasize the consistent decrease in QOL score in patients after radiation therapy. We can assume that the difference arises from the fact that our series contained no patients with malignant tumors who are usually subjected to more aggressive treatment.

The study revealed a pattern that can probably be considered to be universal: the QOL score in patients with benign tumors of the anterior and middle portions of the skull base improved during the first 2 years after surgery and was subsequently stabilized at the same level. The inclusion of radiation therapy into the combination treatment statistically does not worsen QOL in these patients by 3 years and more after surgery, although a temporary decrease in QOL score may occur by the second year after surgery.

Conclusions

The study of QOL in patients with benign tumors affecting the anterior and middle portions of the skull base after surgery and during follow-up revealed that.

1. QOL score was improved within the period up to 2 years after surgery and was subsequently stabilized.
2. Changes in QOL in the postoperative and follow-up periods coincide with the dynamics of patients’ functional status according to the Karnofsky scale and the severity of the neurological deficit on the Rankin scale.
3. Higher QOL scores were observed in patients younger than 30 years of age, both immediately after surgery and during follow-up.
4. Compared to partial resection, radical tumor resection results in a decrease in the QOL score in the early postoperative period and a subsequent improvement.
5. A significant decrease in the QOL score after reoperations justifies the tendency towards maximal radicality of primary surgical intervention.
6. The inclusion of radiation therapy in the combined treatment of patients with radically incurable tumors at least does not reduce QOL score in these patients in the late postoperative period.
The authors conducted an extremely interesting and important follow-up study of surgical and combination treatment of benign tumors localized in the anterior and middle portions of the skull base with allowance for selection of a neurosurgical approach for tumor resection, tumor histological structure, surgical radicality, and postoperative radiation therapy. According to current trends in neuro-oncology (at the turn of the 21st century), the international neurosurgical community supports the thesis that surgical intervention should have its purpose, i.e. the maximal radical tumor resection without making the patient permanently disabled. It is necessary in each particular case to choose the optimal ratio between the surgical radicality and the probable outcome, as well as to evaluate the functional impact of these factors on QOL of patients in the postoperative period.

The following criteria for evaluating patients’ QOL in the preoperative, postoperative, and follow-up periods were selected: the Karnofsky and Rankin scales; the Anterior Skull Base Questionnaire (ASBQ) translated to Russian.

The researchers demonstrated a large group of patients (n=642) operated on at the 6th Department of the Burdenko Neurosurgical Institute, but only 302 out of these patients completed the questionnaire. The results were subsequently analyzed. Most patients were operated on at the Burdenko Neurosurgical Institute; most of them were females of working and socially active age, which emphasizes the need to analyze the impact of neurosurgical or combination treatment on QOL. The patients were divided into 3 groups according to tumor location and the prevailing neurosurgical approach used. Tumors were presented mostly by the grade I and grade II meningiomas (79.6%); the subfrontal approach was frequently used in group 1, the ptoral approach was used in group 2, while the ptoral and/or orbitozygomatic approaches were used in group 3.

The assessment of QOL of patients was performed in 4 stages:
1. In the preoperative period;
2. In the postoperative period;
3. 1—3 months after surgery;
4. 1—6 years after surgery.

The 1st and 2nd stages were evaluated using the Karnofsky and Rankin scales; the 3rd and 4th stages were assessed using the ASBQ questionnaire translated to Russian. The nonparametric statistical methods (the Mann–Whitney U test) were used for statistical analysis.

In all cases, the surgeon tended to perform maximal radical tumor resection without damaging the critical neurovascular structures in order to avoid deterioration in QOL, which eventually resulted in the following outcome: 170 (56.3%) patients underwent radical surgery, 119 (39.4%) had subtotal resection, 10 (3.3%) underwent partial resection, and 3 (1%) had a biopsy.

Ninety-nine patients underwent postoperative radiation therapy. Of them, 56 patients were subjected to SRT in the conventional fractionation regimen and 25 underwent SRT in the hypofractionated regimen; SRS was applied in 5 cases. 12 patients underwent EBRT at the place of residence, and proton beam radiation was used in one case.

REFERENCES


Commentary

The authors conducted an extremely interesting and important follow-up study of surgical and combination treatment of benign tumors localized in the anterior and middle portions of the skull base with allowance for selection of a neurosurgical approach for tumor resection, tumor histological structure, surgical radicality, and postoperative radiation therapy. According to current trends in neuro-oncology (at the turn of the 21st century), the international neurosurgical community supports the thesis that surgical intervention should have its purpose, i.e. the maximal radical tumor resection without making the patient permanently disabled. It is necessary in each particular case to choose the optimal ratio between the surgical radicality and the probable outcome, as well as to evaluate the functional impact of these factors on QOL of patients in the postoperative period.

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PROBLEMS OF NEUROSURGERY NAMED AFTER N.N. BURDENKO 2, 2015
No statistically significant differences were observed when comparing QOL in the preoperative and postoperative periods using the Karnofsky and Rankin scales; however, improvement in the follow-up period was detected both for the scales and according to the ASBQ data. The authors noted that the QOL score was higher in patients younger than 30 years compared to other age groups, but QOL was associated neither with tumor topography nor surgical approach used.

The article especially emphasizes that patients operated on at other institutions had a worse QOL score than the ones operated on at the Burdenko Neurosurgical Institute. The dynamics of patients’ condition depending on extent of surgery is also of interest. Thus, patients who had undergone partial resection had better QOL score in the postoperative period compared to those who had undergone total and subtotal resection, but these scores changed to opposite during the follow-up period. Radiation therapy only reduced the motor activity of patients.

It was shown that the QOL score increases in patients after surgical treatment during 2—3 years after surgery. In patients who had undergone combination treatment, there was a marked decrease in QOL score during 2—3 years after surgery and subsequent improvement in the late postoperative period.

I would like to add that there are few data in modern literature on analysis of QOL in patients with benign tumors of the anterior and middle portions of the skull base after surgical and combination treatment, and this study shows that radical surgery improves QOL compared to nonradical treatment, but only in the long-term period. Thus, both the doctor and the patient should be prepared for a long-term (3 years or more) recovery period.

A.M. Zaytsev (Moscow, Russia)
The thoracic outlet syndrome (TOS) [1—3] or neurovascular compression syndrome [4, 5] is a neurosurgical pathology of the upper thoracic outlet (UTO) that is characterized by a variety of clinical signs caused by multiple factors responsible for compression of a neurovascular bundle (NVB), including the brachial plexus (BP) trunks and subclavian vessels (arteries and veins), in a relatively narrow anatomical space.

The results of recent studies have revealed that factors responsible for NVB compression and important for development of the clinical signs include bone abnormalities (cervical rib, anomaly of the first rib) [6] as well as abnormalities of the fibrous, muscular (anterior scalene muscle syndrome) [7], or musculofibrous structures [8].

In the literature, the clinical symptoms of TOS are mainly discussed in the vascular surgery section [1, 3], and the neurogenic signs are described only in connection with injury of the inferior primary trunk of the brachial plexus [9, 10]. Even though the TOS clinical symptoms are frequently encountered in practice, their analysis is often inadequate, and the diagnostic aspects require a modern approach. Therefore, the topicality of studying the entire spectrum of TOS neurological disorders with allowance for modern diagnostic methods and choosing of an adequate surgical approach ensured satisfactory outcomes in 33 cases.

Keywords: thoracic outlet syndrome, neurovascular compression syndrome, plexopathy, cervical osteochondrosis, vertebrobasilar insufficiency, cervical pains.

Material and Methods

The thoracic outlet syndrome (TOS) [1—3] or neurovascular compression syndrome [4, 5] is a neurosurgical pathology of the upper thoracic outlet (UTO) that is characterized by a variety of clinical signs reflecting multiple factors responsible for compression of a neurovascular bundle in a relatively narrow anatomical space. Even though the clinical symptoms of TOS are frequently encountered in practice, their analysis receives inadequate attention. Both diagnosis of TOS and surgical aspects of its treatment require modern approaches. The study included 46 patients. The main clinical sign was a persistent pain syndrome of the cervico-occipital localization, affecting the shoulder girdle and supra- and infrascapular areas and spreading to the arm, in association with trophic, sensory, and vascular disorders. Spiral computed tomography angiography of the thoracic outlet structures was the main instrumental method. Macro- and micro-factors of compression are the main cause of the neurological symptoms, and their resolving is the main objective of surgical treatment. Surgical approaches were planned depending on the nature and level of injury. A total of 36 patients underwent 42 surgical interventions. The proper assessment of the neurological status in combination with modern paraclinical diagnostic methods and choosing of an adequate surgical approach ensured satisfactory outcomes in 33 cases.

Keywords: thoracic outlet syndrome, neurovascular compression syndrome, plexopathy, cervical osteochondrosis, vertebrobasilar insufficiency, cervical pains.

Material and Methods

An examination algorithm included X-ray of the upper thoracic outlet (UTO) region (28 patients), magnetic resonance imaging (MRI) of the cervical spine (46), electroneuromyography (ENMG) of the brachial plexus trunk (30), and spiral CT angiography (SCTA) of the brachiocephalic vessels and UTO structures (21 patients). Along with instrumental diagnosis, all patients were subject to vascular compression tests (Roos’ stress test, Adson’s maneuver).

The NAV classification proposed by A. Busetto in 2004 was used to process the clinical data. This classification distinguishes three components of TOS: neurogenic (N), arterial (A), and venous (V).

Group 1 included 29 patients (Fig. 1) with combined neurovascular symptoms and prevalence of the vascular component (NAV); of them, 21 patients had predominant signs of arterial circulation impairment (AN type), and 8 patients had signs of venous circulation impairment (VN). Group 2 consisted of 7 patients, predominantly with the neurogenic component (N type). Patients in both groups presented signs of gross NVB compression with pronounced clinical symptoms. Group 3 included 10 TOS patients with mild or non-severe neurological symptoms. They received conservative treatment and were followed-up.

Patients with isolated vascular disorders of A and V types were not included in the study because the urgency of their condition required vascular surgery, regardless of the presence of neurological symptoms.

A total of 42 surgical interventions were performed in 36 patients from groups 1 and 2. Pronounced neurovascular symptoms (NAV) in various combinations (AN, VN, N) were the indications for surgery. The type of surgery depended on the level of NVB injury: the

Material and Methods

The study included 46 patients with TOS: 15 (32.6%) males and 31 (67.4%) females aged between 18 and 65 years.
supraclavicular region, space under the pectoralis minor tendon, or costoclavicular space.

The following approaches developed at the Department of Neurosurgery of the Russian Medical Academy of Postgraduate Education were used in the surgical treatment: supraclavicular posterolateral (SPL) [11], angular axillary (AA) [12], and modified posterior subscapular (MPS) [13] (Fig. 2).

Results and Discussion

Despite obvious signs of neurological disorders, the national literature pays inadequate attention to investigation of TOS. Insufficient awareness of the broad neurological and neurosurgical community of this pathology leads to underestimation of the clinical symptoms and referral of patients to specialists of vascular or other profiles.

Our research was aimed at studying the correlation between TOS clinical manifestations and the data provided by modern instrumental methods. Particular attention was paid to characterization of the pain syndrome and vascular symptoms as well as to the choice of instrumental methods of diagnostics and an adequate surgical technique.

An analysis of the clinical data demonstrated that NVB injuries were more commonly localized in the supraclavicular region and manifested as combined neurovascular symptoms (34 cases).

Since the UTO structures present as a single neurovascular complex, the clinical signs were generalized, and isolated involvement of certain structures was less common (7 cases).

Clinical diagnosis of the NBV lesion level is not always possible; however, isolated pectoralis minor muscle syndrome was diagnosed in eight cases, and compression at the costoclavicular space level was diagnosed in four cases.

Without going into a detailed description of well-known neurological disorders, we will focus on the identified clinical signs characteristic of TOS caused by injuries to the primary and secondary trunks of the brachial plexus as well as their branches in the supraclavian, subclavian, and axillary areas with major vessels passing there. We used a diagnostic algorithm that allowed us to improve the efficacy of TOS treatment.

The neurological picture of TOS develops as a result of a combination of the compressing action of various factors on neurovascular structures in the area to form a variety of neurological manifestations that often resulted in misinterpretation of the obtained data. Numerous patients’ complaints featuring colorful descriptions of the general condition and pain character, not supported by paraclinical diagnostic methods, were regarded as psycho-emotional disorders, and patients were referred to psychoneurologists for treatment.

Pain syndrome is the main complaint of this category of patients, and it was detected in all 46 patients in the study. Pains were localized not only on the inner surface of the shoulder, forearm, and hand (12 patients) but also in the cervico-occipital and interscapular areas, covering the entire shoulder girdle and spreading over the anterior surface of the chest (34 patients).

The clinical diagnosis of the pain syndrome and identification of its origin are often a challenging task. Patients with these complaints are often followed-up and treated by neurologists for cervical osteochondrosis and its complications, humeroscapular neuralgia, and plexopathy; sometimes, these patients are treated by therapists for pseudo cardiac pains.

We followed-up 4 patients who had been previously operated on for cervical disc herniation with unsatisfactory surgery outcomes and 3 patients with signs of anterior scalene muscle syndrome in whom scalenotomy also proved to be ineffective.

Six patients were more concerned with pain in the heart area than with pain in their arms, and they were examined and treated by a cardiologist. Since the results of conservative treatment were unsatisfactory, and paraclinical diagnostic methods failed to clarify the situation, the patients were referred to psychiatrists. Obviously, this extensive pain syndrome in these patients
indicated involvement of all neurovascular structures of the UTO area in a pathological process, while underestimation of the neurological symptoms led to diagnostic mistakes.

An analysis of clinical observations revealed a number of neurological features that helped in differential diagnosis and choosing of an appropriate treatment method.

According to the clinical evaluation, the pain syndrome is constant, localized mainly in the area of the shoulder girdle, upper extremity, and scapula and is exacerbated depending on the body position and physical activity. Patients have to find an easier posture to reduce their sufferings. They bend the affected arm at the elbow and maintain it in this position using various accessories; because of an increase in pain and painful numbness or edema, they avoid lying on the affected side and arbitrarily find a certain constrained posture (e.g., they put a pillow under the affected arm or neck, etc.).

It was noted that the provoking factors exacerbating neurovascular deficit were arms lowered along the body, any minor physical activity, and walking. Therefore, patients have not only to find an easier posture but also to limit their physical activity.

A very informative manipulation may be induction of intense pains and muscle weakness with arms held sideward or raised to and above the horizontal level.

Another feature in examination of patients with TOS is mandatory palpation of the trigger zones located at appropriate myofascial points in the projection of the primary trunks of the brachial plexus and its short branches. Palpation at these points (supra- and subclavian, axillary, and supra- and subscapularis areas) provokes intense pain in the area of the shoulder girdle, scapula, and chest, with pain persisting after completing the test.

The trigger zone of the secondary trunks of the brachial plexus is projected along the deltopectoral groove in the axillary fossa, and the main cause for the development of pain syndrome in these patients (8 patients) is the pectoralis minor tendon (pectoralis minor syndrome). A hyperabduction test, which exacerbates neurovascular deficit, can reveal the injury level. However, it not always possible to perform this test due to the severity of pain syndrome, hypotrophy of the shoulder girdle muscles, and a limited range of movements. In addition, this syndrome in 8 cases was combined with a higher level lesion. Therefore, the palpatory assessment of soreness of the primary and secondary trunks as well as short branches of the brachial plexus indicates involvement of the brachial plexus complex in the pathological process and is a significant landmark in examination of this category of patients. Soreness of these structures is usually combined with hypotrophy of muscles of the shoulder girdle and upper limbs and small muscles of the hand (Fig. 3a, b), which usually leads to functional limitations.

Evaluation of the signs of vascular disorders in the shoulder girdle and upper limb area is very important. The signs manifested as pale skin (primarily in the distal parts of the arm due to impaired blood flow in the subclavian artery, 21 patients) (Fig. 3c) and were accompanied by worsening of muscle weakness and increasing in pain in the arm during physical activity; the results of vascular compression tests revealed signs of impaired arterial blood flow.

The compressing action on the major vessels spread onto the vertebral artery as well. In 12 cases, we detected signs of cerebral circulation disorders in the verteobasilar basin caused by pathology of the V1 segment of the vertebral artery, which gave a peculiar character to the neurological symptoms.

The symptoms of venous circulation impairment that were characterized by cyanosis and edema of the hand and forearm as well as by an accentuated vascular pattern of the upper limb and the anterior surface of the chest wall (Fig. 3d) were observed in eight cases and indicated obstruction of venous outflow through the subclavian vein in the costoclavicular space with the development of collaterals. Furthermore, the symptoms became more pronounced in the upright and sitting positions and disappeared in the prone position as well as with the arm raised above the horizontal level. To sum up the above, it may be noted that the physical signs of circulatory failure may indicate lesion of the major vessels in the UTO area.

Vascular disorders were always accompanied by muscle hypotrophy and neurological deficit that led to functional disorders and worsening of the patients’ quality of life. Therefore, typical complaints of patients and a combination of the neurogenic component with the signs of circulatory failure are convincing evidence in the clinical diagnosis of TOS.

Diagnostic data obtained by instrumental methods are important components in examination of TOS patients. Since SCT angiography data allow one to evaluate both the state of the vascular bed of the brachiocephalic arteries and veins and the muscle and bone structures, routine X-ray and ultrasound are not required, and MRI of the cervical spine and ENMG are used primarily to exclude other pathologies of the cervical spine and nervous structures (herniated disc, various tunnel syndromes, etc.). Therefore, SCT angiography is a preferred instrumental method in diagnosis of TOS.

X-ray semiotics of SCT angiography in TOS is very poorly represented in the literature and requires more in-depth studies with allowance for modern data [14, 15].

An analysis of the results of SCT angiography and their comparison to the intraoperative findings allowed us to divide the factors facilitating NVB compression into macro- and micro-signs. Each of 21 patients who underwent SCT angiography was identified with 27 X-ray macro-signs. They manifested as bony (5), muscular,
and musculofibrous anomalies (13) and also as vascular symptoms (9) (Fig. 4).

Bony anomalies manifested as hypertrophy of the transverse process of the C7 vertebra (Fig. 5a, b, d), an extra cervical rib (Fig. 5b, c), and an abnormality of the anatomical and topographic structure of the first rib (Fig. 5d). These intraoperatively verified anomalies cause changes in the anatomical and topographical relationship of structures in the UTO area and have a compressing effect on NVB.

A retrospective analysis of the course of surgical intervention in correlation with the data of SCT angiography allowed identifying a number of structural features of the interscalene triangle with neurovascular structures passing there. These features were associated with muscular and fibromuscular anomalies and were more common (13 cases) than others.

A change in the interscalene space may occur due to both changes in its constituent structures and the presence of additional structures within the space.

Various anomalies of the anterior scalene muscle (ASM) were observed in 7 cases and manifested as lengthening of its tendinous part, a displacement of its attachment point to the first rib, induration and enlargement of its structure with replacement of muscle fibers with fibrous components that resulted in a loss of the contractile properties of the muscle and a persistent elevated muscle tone. A hypertrophied and sclerotic ASM was a NVB compressing factor (Fig. 6a). In another case, NVB passed deep across ASM, enveloping all its structures. Consequently, the components of irritation and compression were permanent and provoked the clinical symptoms without additional effort. These changes created certain technical difficulties during surgery.

The additional structures included the smallest scalene muscle (SSM) (3 cases) (Fig. 6b), an additional pedicle of the anterior scalene muscle (1) (Fig. 6c), and fibrous bands (2) (Fig. 6d). Passing between the brachial plexus trunks, ASM narrows the interscalene gap and causes constant irritation and compression of NVB.

The radiographic signs of muscular and fibromuscular anomalies will be investigated in the course of accumulation of the clinical data.

Fibrous bands, whose genesis remains unclear, have a compressing effect on both the brachial plexus trunks and the subclavian artery. Figure 7 shows marco-signs of compression found during surgery.

Semiotics of SCT angiography was represented by routine vascular signs: compression of the subclavian artery (SCA) and subclavian vein (SCV) (Fig. 8a, c) in 8 cases; poststenotic aneurysmal dilatation of the third SCA segment (Fig. 8b) in 1 patient with an additional complete cervical rib; various anomalies of the V1 segment of VA (compression, pathological tortuosity, displacement its orifice), which were accompanied by the signs of vertebrobasilar insufficiency (Fig. 8d) (12 cases).

Figure 9 demonstrates intraoperative verifications of vascular anomalies. We would especially like to focus on the vascular anomalies and fibrous bands discovered during surgery whose preoperative diagnostics is impossible. We designated them as compression micro-factors (Fig. 10a—d). The micro-factors play a major role in worsening of neurovascular deficit and provide the clinical picture of pain syndrome with a specific sign — persistent, chronic pain syndrome, sometimes of a deafferentation type, that poorly responds to conservative treatment. It is caused by constant compression of the brachial plexus trunks by hypertrophied abnormal vessels. In our observations, this pain syndrome was accompanied by severe hypotrophy of the shoulder girdle and upper limb muscles.

In our opinion, one of the causes of the development of abnormal vasculature in TOS is deterioration of blood flow in the major vessels that leads to the development of compensatory bypass flow and hypertrophy of the thyrocervical trunk branches and dorsal scapular artery or angiomatosis (6 cases). They can be localized both above and between the trunks of the brachial plexus, causing constant irritation of the nervous structures. In 4 cases, distortions of the anatomic and topographic structure of the UTO region led to involvement of the V1 segment of the vertebral artery in a pathological process that required extending the scope of surgical intervention.
The micro-factors also include fibrous bands (5 cases) that had the compressing effect on both the nervous structures and the subclavian artery, supplementing the neurogenic symptoms with the vascular symptoms (Fig. 11). The compression micro-factors were identified in 11 out of 36 operated patients.

Therefore, the compression macro- and micro-factors are the main cause responsible for the formation of the neurologic symptom complex typical of TOS.

Surgical treatment and choosing of an adequate approach to the UTO structures were planned by comparing the clinical symptoms with the SCT angiography data in order to eliminate macro- and micro-factors of NVB compression.

We performed 42 surgical interventions in 36 patients. The approach type was defined by the level and nature of injury. We used three approaches developed at the Department of Neurosurgery of the Russian Medical Academy of Postgraduate Education. A posterolateral approach (30 operations) was used for decompression and neurolysis of the primary BP trunks and angiolyis of the subclavian vessels and vertebral artery, which enabled elimination of most macro- and micro-factors of compression. A posterior subscapular approach in the sitting position was preferred (4 operations) in the case of bone pathology and clinical signs of injury to the inferior primary trunk of the brachial plexus. An angular approach (8 operations) was used in the case of injury to the secondary BP trunks and axillary vessels with signs of the pectoralis minor syndrome.

A total of 39 surgeries were performed in 33 patients (in 6 cases, concomitant one stage surgery was

Fig. 4. Quantitative characterizations of compression macro-signs in studied patients.

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Fig. 5. Bony signs of compression.

a — hypertrophied transverse processes of the C7 vertebra on both sides; b — extra cervical rib (1), hypertrophied transverse process of the C7 vertebra (2); c — extra cervical ribs on both sides (1 and 2); d — hypertrophied transverse process of the C7 vertebra, abnormal structure of the first rib (2).

Fig. 6. Muscular and musculofibrous anomalies and fibrous bands.

a — ASM hypertrophy; b — SSM (1), subclavian artery (2); c — additional ASM pedicle; d — fibrous bands.
Conducted), and excellent results were obtained in the form of complete regression of the pain syndrome and vascular disorders. Three patients who still experienced symptoms of inferior primary trunk disorders with signs of impaired venous drainage required second surgery.

Complications occurred in 2 patients in the form of Bernard-Horner syndrome (extended scope of surgery, including decompression and angiolysis of the V1 segment of the vertebral artery) that gradually regressed in the postoperative period.

The positive outcomes were achieved due to careful clinical examination of the patients and the choice of the most appropriate surgical approach.
Fig. 10. Micro-factors of NVB compression.

a — angiomatosis; b — hypertrophied artery between the BP trunks; c — compression of the BP trunks by a hypertrophied vein; d — compression of the lower BP trunk: a fibrous adhesion (1), a hypertrophied branch of the dorsal scapular artery (2).

Conclusions

The thoracic outlet syndrome or neurovascular compression syndrome refers to the neurosurgical pathology and is characterized by a variety of clinical signs caused by multiple factors responsible for compression of a neurovascular bundle, such as the brachial plexus trunks and subclavian vessels (arteries and veins), in a relatively narrow anatomical space.

Despite a high occurrence of the clinical symptoms, which are a combination of signs of the neurogenic nature with vascular symptoms, they are not adequately analyzed, and their diagnostic aspects require a modern approach.

The main clinical sign of TOS is pain syndrome that is diffuse in nature, involves the cervico-occipital and interscapular regions, area of the shoulder girdle, anterior chest wall, and upper extremities, and has a number of features that help to differentiate it from other nosological forms.

The primary diagnostic method for identification of the causes of TOS clinical symptoms (macro- and micro-factors of NVB compression) is SCT angiography of the brachiocephalic vessels and UTO structures.

To achieve the maximum clinical outcome, the scope of surgical intervention should include not only decompression of the major vessels and nervous structures but also angiolysis and neurolysis of the brachial plexus trunks. Therefore, treatment of this pathology is the responsibility of neurosurgeons.

REFERENCES

Commentary

In this article, the authors addressed a fairly common disease, thoracic outlet syndrome, whose clinical manifestations are within the competence of various medical specialists because the disease can be caused by bone, muscular, and vascular pathology. The analysis of both national and international publications revealed that this pathology is most often described by vascular surgeons. Works by neurosurgeons are less common. This may be explained by the fact that the clinical symptoms of the disease are in the sphere of interest of vascular surgeons and neurologists, therefore, patients visit primarily these specialists.

The authors draw attention of the neurosurgical community to thoracic outlet syndrome. They provide detailed analysis of the clinical picture and symptoms of the disease, evaluate their significance in the overall picture of the syndrome, analyze and suggest a diagnostic algorithm and a classification on the basis of clinical manifestations, and discuss various surgical approaches.

It should be noted that the authors draw attention to micro-factors that are involved in the syndrome formation but evade preoperative diagnosis, conduct retrospective correlation with the data of preoperative imaging methods, and, finally, based on careful analysis, suggest an adequate, personalized approach to the UTO structures to eliminate the causes of neurovascular bundle compression.

Therefore, “Clinical Diagnostic Features of Surgical Treatment for Thoracic Outlet Syndrome” is extremely important for practicing neurosurgeons. It will enable better understanding of thoracic outlet syndrome, reduce the number of undiagnosed cases, and improve the quality of surgical care to these patients.

A.V. Shitok (Moscow, Russia)
Experience of Using Neuroendoscopy in Treatment of Non-Communicating Hydrocephalus in Infants


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A total of 320 children were operated on for non-communicating hydrocephalus over a period of 10 years (2003—2012). Infant patients amounted to 93.4%, with 29.2% of them being newborns. An endoscopic technique was used to restore the physiological cerebrospinal fluid circulation and manage hydrocephalus without shunt implantation. The positive outcome was observed in 75% of cases. In the other cases, occlusion of the subarachnoid space occurred, which required a combination of neuroendoscopic intervention and shunt implantation. There were no complications and mortality associated with an operative trauma. Keywords: child’s hydrocephalus, isolated fourth ventricle, endoscopic aqueductoplasty, foramina of Monro and Magendie, stent, ventriculoperitoneal shunt, ventriculostomy.

To achieve this goal, we have solved two major problems:
— development and implementation of a set of structural and organizational measures aimed at early diagnosis of progressive hydrocephalus and well-timed neurosurgical care;
— improvement of surgical methods of restoring the physiological CSF circulation in infants with non-communicating hydrocephalus.

Material and Methods

A total of 320 children of all ages were operated on for non-communicating hydrocephalus in the period between 2003 and 2012; the most patients were infants, including newborns (Table 1).

Oclusions of the CSF space were located at one or more of its sites, including the foramen of Monro and lateral ventricles (level I), third ventricle and cerebral aqueduct (level II), fourth ventricle (level III), and subarachnoid space (level IV). Depending on the number of occlusion sites in the CSF pathways, all patients who underwent surgery were divided into two groups: children with occlusion of only one site of the CSF space (single-level non-communicating hydrocephalus, 74.4% of cases) and occlusion of two or more sites (multilevel non-communicating hydrocephalus, 25.6%).

The causes of persistent occlusion of the CSF space included intraventricular hemorrhage (176), inflammatory processes in the CSF system (74), malformations (63), and brain tumors (7).

Organization of specialized medical care. In the case of neurosurgical pathology, in particular progressive hydrocephalus, delivery of specialized medical care in the initial period of the disease is one of the major factors for increasing the care efficacy. The problem of early diagnosis and treatment is of special significance in the...
neonatal period and infancy. We developed and implemented a system of structural and functional organization of stepwise neurosurgical care that plays a significant role in solving this problem (see Flowchart).

As can be seen from the Flowchart, a mobile treatment-and-consultation neurosurgical service, which is a permanently functioning structural unit of a specialized clinic of neonatology, transfers children with neurosurgical pathology from maternity clinics and neonatology units to the clinic or a specialized critical care unit or provides specialized emergency medical care on-site at these clinics.

Specialized departments of neonatology and critical care for newborns and premature infants, which admit patients, are an integrated functional complex that prepares children for surgery and provides medical care afterwards.

**Technical support of surgery.** Rigid endoscopes, Richard Wolf (outer diameter of 3.5 mm) and Karl Storz (outer diameter of 3 mm), were used for neuroendoscopy. Manipulations were carried out using a supratentorial single port approach only, usually through the anterior horn of the lateral ventricle. Within the cerebral ventricles, this method was used irrespective of the site of occlusion and the number of its levels.

When occlusion was localized in the subarachnoid space (level IV), which is usually inaccessible for endoscopic manipulations, additional ventriculoperitoneal bypass surgery was performed using implantable valve drainage systems of various designs.

**Surgical techniques**

The basic principle of a surgical approach in non-communicating hydrocephalus was restoration of the physiological CSF circulation, thereby providing conditions for normalization of natural CSF resorption and compensation of hydrocephalus [7, 8].

Two types of intervention were considered for restoration of the CSF circulation, depending on structural changes in the CSF space.

The first type of surgery was direct elimination of occlusion to restore the natural CSF circulation pathways. Choice of the method of occlusion elimination depended on the localization and structural features of occlusion. We removed blood clots, resected adhesions in the lumen of the lateral ventricles, and performed plastic reconstruction of the foramina of Monro and Magendie, cerebral aqueduct, and cranio cervical junction as well as their stenting.

When intraventricular adhesions sequestered the lumen of the lateral ventricles, resection of the adhesions (Fig. 1) was particularly effective, resulting in restoration of a communication among all ventricular parts.

In the case of mono- and bilateral occlusions as well as stenosis of the foramen of Monro, plasty of the foramen was performed (Fig. 2).

Endoscopic plastic reconstruction of the cerebral aqueduct, aqueductoplasty (Fig. 3), was performed in the case of its membranous occlusion or stenosis and was initially considered as an alternative to high-risk perforation of the third ventricle floor. In the case of the isolated fourth ventricle, aqueductoplasty provides retrograde CSF flow from the ventricle to the superposed parts of the ventricular system [4].

**Figure 4** shows the stages of endoscopic plastic reconstruction of the foramen of Magendie in the case of occlusion of the outlet foramina of the fourth ventricle. An endoscope was moved from the supratentorial approach through the cerebral aqueduct to the fourth ventricle and oriented to the foramen of Magendie. After dissection of adhesions in this area and elimination of

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<th>Table 1. Age distribution of operated children, abs. (%)</th>
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<td><strong>Follow-up period, years</strong></td>
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The flowchart of interactions among structural subdivisions providing neurosurgical care to newborns and infants.
occlusion (see Fig. 4b), the cisterna magna was explored (see Fig. 4c) with dissection of adhesions (if any) in the craniocervical junction region (see Fig. 4e, h) [5, 14].

Multilevel occlusion was eliminated step-by-step, with regard to specific anatomic and morphological changes at each level. For example, in the case of a combination of occlusion of the cerebral aqueduct and fourth ventricular outlet foramina (isolated fourth ventricle), restoration of the physiological CSF passage was performed by a successive combination of plastic reconstruction of the cerebral aqueduct and then the foramen of Magendie, followed by their stenting. For this purpose, a silicone catheter (outer diameter of 2.1 mm, inner diameter of 1.2 mm) was implanted into lumens of the foramina. The catheter extended through all the cerebral ventricles and, if accessible, craniocervical junction to the subarachnoid space and functioned as a stent. The catheter walls were perforated throughout the length. The catheter length was preliminarily calculated using the data of MRI, CT, or neurosonography.

The second intervention type was to form a bypass for CSF flow if occlusion was inaccessible for its direct elimination. Choice of the tactics in this group of interventions depended on the location of occlusion and its relationship with the surrounding anatomical structures.

Septostomy (perforation of the interventricular septum, which was dissected at its most thinned site, usually in the anterior and/or medial parts) was carried out in cases of obliteration of the foramen of Monro (inaccessible for elimination) with separation of both lateral ventricles or in the case of one isolated lateral ventricle (Fig. 5).

Deficit of a communication between the ventricular system and the subarachnoid space upon obliteration of the cerebral aqueduct or fourth ventricle outlet is an indication for third ventriculocisternostomy, which is the creation of CSF outflow from the third ventricle to the interpeduncular and prepontine cisterns by perforating the ventricle floor (Fig. 6).

In the case of the isolated fourth ventricle complicated by complete obliteration of the cerebral aqueduct, which could not be directly eliminated, restoration of a communication between the supratentorial and subtentorial parts of the ventricular system was achieved by the formation of a para-aqueductal bypass for CSF flow between them by two procedures: third-to-fourth ventriculocisternostomy or interventriculostomy.

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**Fig. 1. Resection of intraventricular adhesions.**

a, b — adhesive segmentation of the posterior parts of the right lateral ventricle and multiple adhesions in the lateral ventricles (arrows); c, d — condition after endoscopic resection of adhesions, followed by ventricular drainage using a single shunt.
Fig. 2. Plastic reconstruction of the foramen of Monro.

a — stenosis of the foramen of Monro; b — restoration of the lumen of the foramen of Monro after its plastic reconstruction.

Fig. 3. Aqueductoplasty.

a — membranous occlusion of the cerebral aqueduct; b — perforation of the membrane; c — restored lumen of the cerebral aqueduct; d — stent in the cerebral aqueduct (arrow). Neuroimaging: e — cerebral aqueduct occlusion, preoperative condition (MRI); f — restoration of CSF circulation after plastic reconstruction and stenting of the cerebral aqueduct (MRI, white arrow); g — position of a cerebral aqueduct stent, arrow (3D CT).

The first variant of the manipulation was performed under conditions of the intact ambient cistern (Fig. 7). Passing through the recessus subpinealis of the third ventricle and the cisterna ambiens (ambient cistern), the para-aqueductal CSF outflow into the ambient cistern and then into the fourth ventricle was created by perforation of the superior medullary velum. Operation was supplemented by plastic reconstruction of the foramen of Magendie, thereby forming an additional approach to the subarachnoid space of the cisterna magna [6].

The possibility of interventriculostomy was determined by existing pathological changes in the ventricular system due to its significant dilation. The anterior parts of the dilated fourth ventricle, penetrating into the tentorial opening, contact with the thinned posterior parts of the third and lateral ventricles at the supratentorial level. Because of this, the ambient cistern lumen located therebetween disappears, which enables
Fig. 4. Plastic reconstruction and stenting of the foramen of Magendie and craniocervical junction. Endoscopic image of the surgery stages. 

a — fourth ventricular cavity with hemosiderin deposition; b — adhesiotomy in the foramen of Magendie; c — revision of the cisterna magna; d — vessels of the brain stem; e — revision of the craniocervical junction; f — stoma in the foramen of Magendie area; g — adhesions in the craniocervical junction area; h — adhesiotomy; i — stenting of the craniocervical junction. Neuroimaging of the stent position (white arrow) with respect to the brain stem (black arrow) and the skull after surgery; j — IR; k, l — MRI.

Creating a communication between the fourth ventricle and the posterior ventricular parts located above and supratentorially by perforation of their adjoining walls.

Third-to-fourth-ventriculocisternostomy created CSF flow between the isolated fourth and third ventricles (Fig. 8). An anastomosis formed between the ventricles usually remained functioning, and no stent implantation was required to support it.

During latero-fourth-interventriculostomy, CSF flow between the fourth and lateral ventricles was formed by perforating their adjoined thinned walls (Fig. 9). In this case, stent implantation was usually required to prevent occlusion recurrence.

In both operation types, either with direct elimination of occlusion or creation of a CSF bypass, the CSF circulation within the ventricular system was restored; however, the craniocervical junction or subarachnoid space remained blocked in some cases. In these cases, there were indications for supplementing endoscopic intervention with implantation of a ventriculoperitoneal shunt to provide CSF outflow and, thereby, normalize intracranial pressure. Shunting was used to solve as much
as possible the problem of drainage of not only the cerebral ventricles but also the subarachnoid space using a panventriculocisterno-peritoneal shunt (Fig. 10). The use of endoscopy allowed optimization of shunt implantation. A perforated ventricular catheter of the shunt was passed from the anterior horn of the lateral ventricle through the third ventricle and cerebral aqueduct to the fourth ventricle cavity under endoscopic control. If the cisterna magna and cervical subarachnoid space were accessible, the catheter was passed further to their lumen. In this case, the ventricular shunt catheter situated in anatomical narrowings of the ventricular system acts simultaneously as a stent of the narrowings.

Results and Discussion

In our case, infants who amounted to 93% in the second half of the observation period (2008—2012) represented the major group. In this case, the number of newborns among them increased more than 3 times (see Table 1). The undertaken structural and organizational measures reduced the period between birth of a child and delivery of specialized care to several days or even hours.

Outcomes of interventions, which are shown in Tables 2 and 3, confirmed the adequacy of the criteria used to choose a surgical technique matching the form of occlusion, its localization, and structure. Both intervention types enable achieving compensation of hydrocephalus, providing CSF resorption, and significantly reduce the indications for shunt implantation, thereby avoiding the risk of frequent shunt-associated complications, which require multiple repeated interventions (revisions).

At the first stage of the work, the extent of intervention in the case of single-level variants of non-communicating hydrocephalus was limited to restoration of the intraventricular CSF circulation without eliminating
Fig. 7. Third-to-fourth ventriculocisternostomy

a — scheme of the main stages of endoscopic third-to-fourth ventriculocisternostomy. Arrow 1 — posterior third-ventriculocisternostomy (through the recessus subpinealis to the cisterna ambiens), Arrow 2 — fourth-ventriculocisternostomy (from the cisterna ambiens through the superior medullary velum to the cavity of the fourth ventricle; b — the main stages of planned intervention — posterior third-ventriculocisternostomy from the cisterna ambiens (dashed arrow) through the cisterna ambiens, fourth-ventriculocisternostomy (white arrow), plastic reconstruction of the foramen of Magendie (black arrow), c — condition after surgery, stoma of the floor the third ventricle (white arrow); restoration of CSF circulation after plastic reconstruction of the foramen of Magendie (black arrow).

Fig. 8. Third-to-fourth interventriculostomy.

a — isolated fourth ventricle, MRI (sagittal plane), preoperative state (the arrow indicates the endoscope path for creating an anastomosis between the ventricles), b — postoperative state, decreased volume of the fourth ventricle.

occlusion of the cerebral aqueduct or foramen of Magendie. CSF outflow into the subarachnoid space was achieved through the creation of a bypass for CSF flow by perforating the floor of the third ventricle (third ventriculostomy). As a result, compensation of hydrocephalus was achieved in 44% of cases (see Table 2). Along with other authors [21, 22], we believe that blockage of the basal cisterns due to adhesions associated with present or past arachnoiditis was one of the major causes of lacking a positive effect of third ventriculostomy in other cases.

At subsequent phases of the work, we still extensively used third ventriculocisternostomy but combined it with direct elimination of occlusion at sites of anatomical narrowings (cerebral aqueduct, foramen of Magendie, and also craniocervical junction) by means of their plastic reconstruction and stenting. This provided more extensive and easier CSF flow to the subarachnoid space. Alteration of a surgical approach resulted in an increased number of cases with achieved compensation of hydrocephalus up to 75%. The efficacy of this tactics is confirmed by numerous publications [3, 6, 9—13, 15—20, 23—26].

In our cases, multilevel occlusion, when neuroendoscopy is of absolute priority, was observed in every fourth child (25.6%). In almost all cases with both
**Fig. 9. Latero-fourth-interventriculostomy.**

a — MRI of the isolated fourth ventricle, b — operation scheme; c — endoscopic picture before formation of a stoma, d — endoscopic picture after formation of the stoma; e — postoperative MRI of the brain, decreased volume of the cerebral ventricles; f — MR image of the interventricular stoma (arrow); g — a catheter implanted between the lateral and fourth ventricles (arrow).

**Fig. 10. Panventriculocisterno-peritoneal shunting in the case of isolated fourth ventricle.**

a — isolated fourth ventricle before surgery; b — state after plastic reconstruction of the cerebral aqueduct and passing a ventricular shunt catheter through it, volumes of the lateral and fourth ventricles are decreased; c — 3D CT image of a panventriculocisterno-peritoneal shunt.
single-level and multilevel occlusion, restoration of CSF circulation within the ventricles was achieved (99.6 and 98.8%, respectively).

However, disturbance of CSF flow during passage into the subarachnoid space or within it retained in both occlusion forms in some patients. This was usually caused by a posthemorrhagic or postinfectious arachnoiditis accompanied by an adhesive process in the subarachnoid space. This caused blocking subarachnoid space patency in its certain parts and hindering CSF resorption. Under these conditions, there was the need for additional implantation of a shunt to stabilize hydrocephalus, which occurred more often in the case of multilevel occlusion compared to single-level one (46.34 and 25.2%, respectively).

It should be noted that the number of shunt implantation complications requiring repeated interventions (revisions) also prevailed in the case of multilevel occlusion (21 and 13.9% of cases, respectively). In this case, almost a sixfold decrease in the number of shunt revisions was observed during the second observation period (2008—2012) compared to the first period (see Tables 2 and 3).

Postoperative complications of endoscopic interventions, including both wound complications (liquorrhea, ventriculitis, subdural or subcutaneous accumulation of CSF, stent dislocation) and neurological complications (epileptiform seizures, strabismus) were observed only in single cases and were transient. In general, these complications occurred in 11% of cases. There was no mortality directly associated with the surgery. Eight children died because of various somatic pathologies associated with prematurity.

**Conclusions**

The structural and organizational scheme that was developed and implemented in practice has proved its efficacy in the delivery of specialized medical care, in particular in the case of non-communicating hydrocephalus at the earliest stages of the disease, including the neonatal period.

The use of neuroendoscopy in surgical treatment of the single-level form of non-communicating hydrocephalus in most cases allows for renewal of physiological CSF circulation. In the case of multilevel occlusion, this technique is of absolute priority.

Endoscopic surgery combines a high efficacy and a minimal risk of injury, which makes this technique the method of choice for children, including infants and newborns.

**REFERENCES**


This paper focuses on treatment of neonatal and infantile complex hydrocephalus that is one of the most important aspects of pediatric neurosurgery. Parenchymal and intraventricular hemorrhage causing this pathology as well as ventriculitis complicating the pathology in many cases (especially in premature infants) lead to complex disorders of CSF circulation with formation of porencephalic cysts as well as multilevel obstruction in the ventricles and subarachnoid spaces with septation, sequestration, and formation of isolated and tension CSF cysts. Treatment of these children by implantation of shunt systems requires complex multicomponent devices, sometimes even more than one, with various Y-connectors, adapters, etc. These implants are significantly more prone to obstruction and infection than simple linear systems. Their revision and reinstallation are required in up to 2/3 of infants during 1—1.5 years after operation and usually are performed more than once. Because of unresolved edema and intracranial hypertension, these children are delayed in their development to a greater extent than it could be in the case of one well-timed, final, and successful intervention.

The authors’ idea is to eliminate all levels of occlusion and restore the natural physiological CSF circulation pathways. For this purpose, they endoscopically fenestrate newly formed membranes and septa, or (if the above procedure is impossible, or there is a risk of reocclusion) implant silicone stents. If this does not work, they use endoscopic ventriculostomy of the third ventricle, and, if it is still ineffective, they implant a simple linear valve shunt in the cerebral ventricles. The authors reasonably indicate importance of shifting the surgery time to the earliest period of the disease, before the beginning of the irreversible changes in brain tissue compliance and other problems associated with previous improper shunting. In recent years, after establishing a mobile treatment-and-consultation neurosurgical service and a connection between maternity clinics and critical care and neonatology departments, they could increase three times the percentage of children who underwent surgery before the age of 1 month. The practicability of this organization of medical care can be seen from comparison of the results in two groups of children before and after 2008, when the system was launched. The percentage of children with shunted single-level occlusion who later needed shunt revision decreased four times, and the percentage of children who did not need shunting at all increased almost twice. The authors do not emphasize this fact, but given that they limit the data to 2012, it may be concluded that the follow-up period is apparently at least 1 year.

If we go back to the significance of endoscopic techniques in resolving multilevel occlusion, the result obtained by the authors is phenomenal: more than a half of children live without a shunt; in cases where there was a need in using shunts, only 1/5 of patients needed shunt revision.

Commentary
The paper does not discuss repeated endoscopic procedures that are required in these patients. It should be noted that the need for these endoscopic procedures arises with a probability of 0.19—0.3 per year, and this fact is reported in the literature both cited and not cited by the authors. It should also be noted that mortality in the cases observed by authors is generally higher (4%) compared to the literature data. The authors do not discuss this issue, but it seems that this is related to the initially grave condition of small-for-date and severely affected infants who prevailed in this work. However, it seems strange that other complications were rare and observed only in 11% of cases. Unfortunately, they were not discussed because treatment of some of them, e.g., ventriculitis and stent migration, apparently required some sort of re-intervention, while complications such as strabismus were probably related to perforation of the anterior medullary velum in aqueductoplasty. These issues are important for professionals who want to reproduce the described technology.

Anyway, the work will arouse interest, and I would like to congratulate the authors on the obtained results.

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De Novo Cerebral Aneurysms

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**Objective.** The study was aimed at substantiating the advisability and time of control angiographic examination of patients operated on for cerebral aneurysms to rule out de novo aneurysm formation. **Material and methods.** The results of angiographic examination (cerebral angiography and SCT angiography) of 43 patients (aged 14 to 56 years) with cerebral aneurysms operated on at the Burdenko Neurosurgical Institute in 1995—2012 were analyzed. The follow-up duration ranged 1 to 14 years after surgery (mean duration was 5 years). **Results.** Control angiographic examination revealed de novo aneurysms in 7 (16.2%) patients. A total of 8 de novo aneurysms were detected (in one case two aneurysms formed). All aneurysms, both previously operated and de novo ones, were localized within the anterior parts of the circle of Willis. De novo aneurysms were clipped in 5 cases; the cavity of de novo aneurysm was occluded with coils in one case. One patient with a small aneurysm of the middle cerebral artery refused surgery. Neither lethal nor unfavorable outcomes were observed. **Conclusion.** The risk groups for de novo aneurysm formation are likely to be as follows: 1) young smokers with hypertension; 2) patients who developed clinical signs of the disease at young age; 3) patients who underwent proximal exclusion of the main artery; and 4) patients with multiple and familial forms of the pathology. Angiographic follow-up (SCT angiography or MR angiography) for 1—3 years is recommended for these patients.

**Keywords:** cerebral aneurysm, de novo aneurysm, newly formed aneurysm, subarachnoid hemorrhage.

In 1964, C. Graf and W. Hamby [10] for the first time reported a case of de novo aneurysm of the middle cerebral artery (MCA). Later, formation of new aneurysms (de novo) in the long-term period after complete aneurysm clipping has been repeatedly confirmed [1, 2, 4, 5, 7—13, 15, 17, 18, 20, 22, 24, 26, 28—32].

According to H. Yamakawa et al. (1997) and other authors [1, 2, 5, 21, 31—33], de novo aneurysm rupture is the major cause of delayed repeated subarachnoid hemorrhage (SAH) in patients with completely clipped aneurysm. The risk of this hemorrhage is 2% during the first 10 years after surgery and 9% after 20 years [5]. M. Wermer et al. [31] reported the absence of repeated SAH from a de novo aneurysm during the first 33 months after surgery.

In most cases, de novo aneurysms are detected during examination after repeated hemorrhage. According to N. Rahman et al. [21], among 11 patients with newly formed aneurysms, 8 patients were diagnosed with aneurysms after SAH recurrence.

According to various sources [4, 29, 31], the incidence rate of de novo aneurysms is 1.5 to 16% of cases. The probability of formation of a new aneurysm within 1 year after surgery for aneurysm ranges 0.8 to 2.2% [4, 28].

The time of de novo aneurysm formation varies from 3 to 20 years [31].

The objective of this work is to substantiate the advisability and time of angiographic examination of patients operated on for cerebral aneurysms to rule out the formation of new aneurysms.

**Material and Methods**

The data of angiographic examination (cerebral angiography and spiral computed angiography (SCT AG)) of 43 patients (24 females and 19 males aged 14 to 56 years) with cerebral aneurysms operated on at the Burdenko Neurosurgical Institute in the period from 1995 to 2012 were analyzed. The follow-up period ranged 1 to 14 years after surgery (5 years, on average). Initially, 38 patients had solitary aneurysm, and 5 patients had multiple aneurysms.

**Results and Discussion**

In the study series, control angiographic examination revealed the formation of new aneurysms in 7 (16.2%) patients (5 females and 2 males). Along with the analytical data of M. Wermer et al. [31], this is the highest rate compared to that in other studies. Significant differences in the published data and a small number of publications on this issue are indicative of the need for further research. A total of 8 new aneurysms were detected (in one case, two aneurysms formed). The aneurysms had a different location than previously operated ones, except one that formed next to the neck of the clipped aneurysm. All aneurysms, both previously operated on and newly formed ones, were located within the anterior parts of the circle of Willis. New aneurysms were clipped in 5 cases, and the cavity of a new aneurysm was occluded with coils in one case. One patient with a small aneurysm of the MCA refused surgery. There were no lethal and adverse outcomes.

Some authors [1, 7, 28, 32] distinguish two types of de novo aneurysms: those growing at the site of previously clipped aneurysms, and de novo aneurysms with a different, rather than the initial, localization. J. Rinne and J. Hemesniemi believe that aneurysms arising from the neck portion after partial clipping and aneurysms formed due to growth of previously observed funnel-
shaped bulges are not de novo aneurysms [22]. We be-
lieved that only newly formed aneurysms of a different
localization should be considered as “true” de novo an-
eurysms. Formation of aneurysms in the neck portion
of a clipped aneurysm should be considered as regrowth
of the aneurysm. This growth can originate from a small
segment of a thinned neck portion not covered by the clip
jaws. This, in turn, may be due to the fact that clip jaws
are not always positioned strictly in the neck line during
aneurysm clipping. However, observations of both aneu-
rysm growth from the neck portion of clipped aneurysms
and formation of de novo aneurysms that are not related
to previous aneurysms in terms of their localization are
important for both practical matters and studying the eti-
ology and pathogenesis of aneurysms.

Initially, de novo aneurysms were most often detected
in connection with repeated SAHs. The development of
the de novo aneurysm concept and widespread imple-
mentation of non-invasive neuroimaging techniques
made it possible to identify asymptomatic de novo aneu-
rysms.

Since 2001—2002, we have recommended almost all
patients operated on at the Burdenko Neurosurgical In-
stitute for cerebral aneurysms to undergo SCT angiogra-
phy within 1 to 3 years after surgery, depending on the
patient age, surgery outcome, form of pathology (multi-
ple, familial), and confounding factors (smoking, hyper-
tension).

In this series, 2 cases of de novo aneurysms were
found after repeated hemorrhage and 5 cases during dy-
namic angiography (SCT AG).

Case report

A 32-year-old female patient D. was admitted to
the Burdenko Neurosurgical Institute with the diagnosis
of aneurysm of the supraclinoid segment of the right in-
ternal carotid artery (ICA); SAH (the 10th day). The se-
verity of the condition was characterized by Hunt and
Hess grade III. The patient was 25 weeks pregnant
and had hypertensive disease. SCT AG revealed an aneu-ysm of the supraclinoid segment of the right ICA. There
were no aneurysms at other sites (Fig. 1).

08.02.07, the patient underwent surgery including
clipping of the aneurysm of the supraclinoid segment of
the right ICA. The patient withstood the operation with-
out complications and was discharged in satisfactory
condition. Later on, successful delivery was performed at
the place of residence. SCT AG of the head in 3 years was
recommended.

SCT AG in 2010 revealed that the aneurysm of the
right internal carotid artery was not filled. There were no
de novo aneurysms. However, some bulging of the
left MCA bifurcation was observed (Fig. 2). Repeated
computed AG in 2012 revealed the formation of a new
aneurysm of the bifurcation of the left MCA (Fig. 3).

![Fig. 1. SCT AG (with 3D-reconstruction) of a female patient D. in 2007. Aneurysm of the supraclinoid segment of the right ICA (An. ICA) can be seen. The arrow indicates the bifurcation of the left MCA without aneurysm.](image1)

![Fig. 2. SCT AG (with 3D-reconstruction) of a female patient D. in 2010. Aneurysm of the supraclinoid segment of the right ICA is excluded by clipping. The arrow indicates the bifurcation of the left MCA, where some bulging was detected compared to the data of 2007.](image2)

![Fig. 3. SCT AG (with 3D-reconstruction) of a female patient D. in 2012. Newly formed aneurysm (de novo aneurysm) can be seen at the bifurcation area of the left MCA. Right ICA aneurysm is excluded by clipping.](image3)
A new aneurysm of the anterior communicating artery formed in one patient 1 year after occlusion of the ICA.

**Case report**

A 28-year-old female patient B. was admitted to the Burdenko Neurosurgical Institute with the diagnosis of giant, partially thrombosed aneurysm of the left ICA bifurcation in 2004.

Surgery for clipping of the *de novo* aneurysm of the bifurcation of the left MCA was performed on 03.10.12. The operation revealed that the aneurysm had thin walls. The patient was discharged home in good condition.

This case demonstrates not only the fact of *de novo* aneurysm formation but also the possibility to prevent recurrent SAH characterized by a high mortality level. Furthermore, the case confirms the acquired nature of the aneurysm.

Several publications [6, 9, 11, 14, 16, 19, 23] have indicated proximal clipping of the main cerebral arteries as one of the factors contributing to *de novo* aneurysm formation. In our series, a new aneurysm of the anterior communicating artery formed in one patient 1 year after occlusion of the ICA.

**Fig. 4. CT of the brain and a left-sided carotid angiogram of a female patient B.**

a — the arrow indicates the contour of aneurysm in a CT image; b — the arrow indicates a functioning part of a giant aneurysm of the left ICA bifurcation.

**Fig. 5. Angiogram and craniogram of a female patient B. after ICA occlusion using a balloon.**

a — right-sided craniogram; the AComA area is visualized; no aneurysm is observed. The arrow indicates a contrast-enhanced part of an aneurysm of the left ICA bifurcation. Left ACA and MCA are well filled; b — a balloon in the lumen of the left ICA can be seen.
medical advice. In recent years, the patient experienced frequent headaches. A giant, partially thrombosed aneurysm of the left internal carotid artery was suggested based on CT of the brain (Fig. 4a). The neurological status at admission was normal. Survey angiography confirmed the presence of an aneurysm (see Fig. 4b). No aneurysms were identified at other sites (Fig. 5a). Surgery was performed that included occlusion of the left ICA at the petrous segment level using a balloon. An occlusive test was performed for 15 min; no focal symptoms were observed. The balloon was filled with 0.5 mL of gel and detached. The control angiography of the right carotid and left vertebral arteries demonstrated a reduction in the contrast-enhanced portion of the aneurysm and satisfactory filling of the left ICA territory (see Fig. 5). The patient withstood the operation without complications. The control angiography 1 year after surgery revealed an aneurysm of the anterior cerebral artery—anterior communicating artery (ACA—AComA) on the right (Fig. 6). Surgery was performed on 27.05.05. The walls of the fusiform aneurysm of the right ACA—AComA were reinforced with surgical gauze and adhesive (Fig. 7). The patient withstood the operation without complications. The

### Time of de novo aneurysm detection

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years*</th>
<th>Cause of detection</th>
<th>Time of detection, years</th>
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<td>Dynamic control</td>
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<td>2</td>
<td>28</td>
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<td>7</td>
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Note. * — patient’s age at the time of detection of the first aneurysm
annual control magnetic resonance angiography, MR AG and SCT AG, revealed no signs of aneurysm growth. Three years after the second operation, the patient gave birth to a baby.

This case may indicate interaction between the hemodynamic factor and structural changes in the vascular wall in developing a new aneurysm. According to G. Dyste et al. [6], formation of a de novo aneurysm after ICA occlusion occurs in 4% of cases, which is associated with the hemodynamic stress.

Many authors [4, 13, 18, 21, 22, 33] attribute familial and multiple forms of the pathology, along with hypertensive disease and smoking, to the risk factors of de novo aneurysm formation. Out of 7 patients detected with de novo aneurysms, only 1 patient initially had multiple aneurysms. No cases of the familial form were observed. Six patients suffered from hypertensive disease. Five patients were long-term smokers.

New aneurysms were detected during dynamic angiographic control 1, 2, 3, 5, and 7 years after surgical treatment. It should be noted that a female patient who was detected with a new aneurysm after 7 years did not undergo dynamic angiographic control before this period, therefore, the aneurysm could form earlier. The time scale for diagnosis of aneurysms in patients who suffered repeated hemorrhage was large and ranged 3 to 14 years (see Table).

Rare cases of early formation of a new aneurysm were reported [25, 27]. K. Schebesch et al. [25] published a case of de novo aneurysm formation in the bifurcation of the basilar artery in a 37-year-old patient 8 weeks after clipping of an ACA aneurysm. J. Sim et al. [27] presented a case of earlier formation of two de novo aneurysms of the A2 segment of the left ICA in a 38-year-old patient as early as 30 days after surgery for a ruptured aneurysm of the left ICA. According to M. Wermer et al. [31], the period of de novo aneurysm formation ranges 3 to 20 years. It should be noted that these terms were determined according to the results of examination of patients who had repeated hemorrhage. Thus, it was the time of SAH from a new aneurysm, rather than a period within which the new aneurysm formed. Widespread use of non-invasive neuroimaging techniques (CT AG and MR AG) will allow for more precise determination of the time of de novo aneurysm formation in the future.

Conclusions

Since either we or the literature lacks statistically significant comparative studies on this issue, groups of patients with high risk of new aneurysm formation may be distinguished only tentatively.

These groups are as follows:
1. Young smokers with hypertensive disease.
2. Patients who developed clinical manifestations of the disease at young age (under 50 years).
3. Patients who underwent proximal exclusion of the main artery.
4. Patients with multiple cerebral aneurysms and the familial form of the pathology.

Given the time of detection of new aneurysms and repeated hemorrhage from them, dynamic angiographic control (SCT AG or MR AG) is indicated within 1—3 years. The frequency of this control is chosen individually, depending on the risk factors for aneurysm formation (young age, gender, hypertension, smoking, etc.).

The suggested tactics reduces the risk of delayed recurrent SAHs and improves treatment outcomes in patients with cerebral aneurysms.

REFERENCES

New aneurysms form in a relatively small number of patients after successful treatment (clipping or endovascular occlusion) of ruptured or pre-hemorrhagic cerebral arterial aneurysms. Newly formed aneurysms are divided into de novo ones (an aneurysm distant from the first aneurysm), regrowth (recurrent growth of an operated aneurysm), and additional aneurysms (retrospectively detected aneurysm that was not detected during initial examination). After the first report of a “new aneurysm” in 1964, a large number of studies on epidemiological aspects of these aneurysms have been published. The risk of de novo aneurysm formation is 0.28—1.62% per year after detection of the “first” aneurysm [1].

In the article by A.S. Kheyreddin et al., 7 patients with 8 newly formed aneurysms detected during the control cerebral angiography (5 cases) and after repeated intracranial hemorrhage (2) are described. Of these aneurysms, regrowth in the neck area of a clipped aneurysm occurred in one case, while the remaining 7 cases were considered as de novo aneurysms. Based on their own observations and previously published data, the authors provided recommendations for conducting angiographic control in the postoperative period and listed the well-known risk factors for arterial aneurysm formation.

The invasive surgical tactics of treatment of de novo aneurysms used by the authors in 6 of the 7 cases is reasonable, since the neurosurgeons’ attitude to these aneurysms is currently more cautious and aggressive, although this approach is still not clearly substantiated.

The question whether the rate of hemorrhage from a de novo aneurysm is similar to the probability of hemorrhage from small occasionally detected saccular aneurysms remains still open. Published data show a relatively high risk of intracranial hemorrhage from de novo aneurysms, but the cause of this discrepancy in the rate of intracranial hemorrhages remains unknown [2].

The effort to shed some light on the existing unsolved issues of the natural course and surgical treatment of de novo aneurysms reflects credit on the authors. Subsequent collection of clinical data and their generalization will expand the understanding of the development, clinical manifestations, minimally invasive diagnostic methods, and surgical methods of treatment of de novo aneurysms.

REFERENCES


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The Effectiveness of a HyperHAES Hypertonic Iso-oncotic Plasma Solution in Achieving Stable Intracranial Hypotension in Endoscopic Endonasal Transsphenoidal Adenomectomy as an Alternative to Invasive External Lumbar Drainage


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Transnasal surgeries have been performed at the N.N. Burdenko Neurosurgical Institute for more than 30 years. Prior to 2006, all operations had been microscopically-controlled (with or without endoscopic assistance). More than 7,000 operations had been performed over that period of time. Since 2006, all transnasal surgeries at the clinic have been entirely endoscopically-controlled. More than 3,500 operations have been performed thus far. Approximately 70% of tumors resected using the transnasal approach are pituitary adenomas, i.e. tumors with well-defined capsules. In our practice, the percentage of tumors without suprasellar spread does not exceed 10%.

Almost from the beginning, it became clear that the transnasal approach requires control over the position of the suprasellar part of the tumor. Initially, only lumbar punctures with introduction of 20.0—30.0 mL of air were used, which allowed correlating positions of a tool and the suprasellar part of the tumor capsule using lateral craniography with an image converter. Since an operating microscope limits the operative field to the sellar cavity only, a technique of controlled intracranial hypertension was developed to improve visualization of the suprasellar parts of the tumor. The technique enables bringing the superior parts of the tumor capsule and tumor remnants down to the sellar cavity using endolumbar injection of saline via an external lumbar drainage [1, 9].

Adoption of endoscopically-controlled surgery revealed the opposite requirement: the tumor capsule bulging to the sellar cavity prevented inspecting all cavity portions, detecting and resecting tumor remnants, and reducing the risk of damage to the capsule. The simplest and most effective method of visualization of the entire surface of the tumor capsule appeared to be removal of the cerebrospinal fluid (CSF) into a lumbar drainage and achieving of intracranial hypotension without or in a combination with hyperventilation or by placing the patient in the semi-sitting position [5]. The position of the tumor capsule, depending on intracranial pressure, is schematically presented in Figure 1. The use of intracranial hypotension had two more advantages: the possibility of a fast reduction in venous pressure in the cavernous and intracavernous sinuses in the case of venous bleeding from them as well as the possibility of “dry” reconstructive surgery for skull base defects under conditions of intraoperative liquorrhoea. Therefore, over the past 8 years, almost all transnasal surgeries were performed using an external lumbar drainage.

As an invasive technique, lumbar drainage may be associated with a number of serious complications: liquor-dynamic and dislocation complications, infectious complications, pneumocephalus, changes in the CSF composition, post-puncture syndrome, hemorrhagic complications, and direct injury. The risk of postoperative meningitis ranged from 1.2 to 8%, depending on the tumor size and surgery features [10].

Administration of a HyperHAES infusion solution (Fresenius Kabi, Germany), which is a 7.2% NaCl solution in 6% hydroxyethyl starch (HES) 200/0.5 [2, 6—8], is another variant of reducing intracranial pressure...
This plasma substitute medicine is a hypertonic iso-osmotic solution. Its osmolarity is 2,464 mosmol/L; however, in spite of this, the solution may be injected into a peripheral vein (information is available in the Vidal reference books at www.vidal.ru), which is very convenient for endoscopic endonasal transsphenoidal adenectomy that rarely requires central venous catheterization. Because of the high HyperHAES osmolarity (especially in the case of its rapid administration), the liquid (mostly from the intercellular space) quickly moves into blood vessels and, thereby, increases the volume of circulating blood. As a result, blood pressure (BP) and cardiac output rapidly increase, and perfusion of tissues, including the brain, is enhanced. In the case of preserved autoregulation of cerebral vessels, increased cerebral perfusion pressure leads to their vasoconstriction and a reduction in brain blood filling and intracranial pressure. The HyperHAES circulating half-life, $T_{1/2}$, is about 4 h. By the beginning of the study, the medicine had been already extensively used at our clinic to reduce intracranial pressure both at different stages of neurosurgery and in critical care procedures after surgery [2, 4].

**Material and Methods**

A total of 84 patients aged 49.7±1.6 years were included in the study. The majority of patients, 82 (97.6%), underwent removal of various pituitary adenomas. In 2 cases, the tumor had a different histological pattern: intracapsular removal of endosuprasellar craniopharyngioma was performed in 1 (1.2%) case, and resection of chordoma was carried out in 1 (1.2%) case. Suprasellar spread of pituitary adenomas was observed in 66 (80.5%) out of 82 patients with pituitary adenomas. Endosellar pituitary adenomas occurred in 16 (19%) patients.

Tumors were removed via the standard endoscopic endonasal transsphenoidal approach [3]. Typically, the removal was intracapsular, i.e. excision of the tumor capsule was not planned before surgery.

During the tumor approach stage, all patients in the study group were intravenously injected with 250 mL of HyperHAES for 10—15 min. During the first 20 surgeries, a lumbar drainage was routinely placed to patients, as it had been placed in previous years. However, in contrast to the common practice, the drainage remained closed until the end of operation, since the tumor capsule was completely spread in all cases after HyperHAES infusion, and additional CSF drainage was not required. This rendered placement of a lumbar drainage unnecessary in all subsequent 64 operations, during which complete spreading of the tumor capsule was also observed throughout surgery.

Intracranial pressure (ICP) in the first 20 patients was continuously monitored throughout surgery by means of an invasive pressure sensor connected to a

**Fig. 1. Schematic representation of a change in the tumor capsule position, depending on the ICP value.**

- **a** — bulging of the tumor capsule into the sellar cavity associated with normal or increased intracranial pressure;
- **b** — spreading of the capsule associated with intracranial hypotension;
- **c** — intraoperative photos. The suprasellar part of the tumor capsule with tumor remnants bulging into the sellar cavity;
- **d** — intraoperative photos. Visualization of the tumor capsule cavity after its spreading and removal of tumor remnants.
lumbar drainage. The ICP values were recorded three times: before and after HyperHAES infusion and at the end of surgery. The lumbar drainage remained closed throughout operation. Basic hemodynamic parameters, the mean blood pressure (MBP) and mean heart rate (MHR), were recorded alongside with ICP. All patients were tested for the content of major plasma electrolytes (Na\(^+\), K\(^+\), cardiac glycosides, Cl\(^-\)) preoperatively, after HyperHAES infusion, and on the day after surgery. The BIS depth of anesthesia was also monitored in all patients.

**Results**

**Hemodynamic parameters**

During surgery, the hemodynamic parameters were stable within the normal range in all patients in this group. There were no significant fluctuations of the hemodynamic parameters at the primary points (before and after HyperHAES infusion, at the end of operation). The values were as follows: MBP was 94.47±1.58 mm Hg (at the beginning of infusion), 98.4±2.47 mm Hg (after infusion), and 94.01±2.56 mm Hg (at the end of operation), respectively; MHR at the primary points was 75.55±1.33, 80.9±1.44, and 77.9±1.3 per minute, respectively. A small increase in MBP (4.1%) and MHR (7%) was observed after HyperHAES infusion. It should be noted that the end of HyperHAES infusion coincided with the most painful phase of operation, approaching to the tumor, which might also affect this minor change in the hemodynamic parameters.

**ICP dynamics**

During ICP monitoring, a distinct ICP decrease by 8.46 mm Hg, on average, was observed (Fig. 2). The ICP values were 10.96±0.7 mm Hg (before infusions), 4.27±0.98 mm Hg (immediately after intravenous infusion of HyperHAES), and 2.5±1.04 mm Hg (at the end of operation). It should be noted that, in addition to HyperHAES, other factors might affect the reduction in ICP: patient’s semi-sitting position and propofol action.

After HyperHAES infusion, the electrolyte composition of plasma reversibly changed, but normalized within the first 24 hours.

**Baseline electrolyte parameters**

The initial preoperative plasma electrolyte levels in patients did not exceed the normal limits and were as follows: 142.95±0.55 mmol/L Na\(^+\), 4.36±0.09 mmol/L K\(^+\), and 105.45±0.54 mmol/L Cl\(^-\).

Changes in electrolytes immediately after solution infusion

HyperHAES injection resulted in an increase in the Na\(^+\) level by 5 mmol/L (on average) above the normal value and amounted to 150±0.71 mmol/L. The level of Cl\(^-\) increased by 12 mmol/L, on average, and
was 118.3±1.06 mmol/L. The level of K⁺, on the contrary, declined but remained within the normal range and amounted to 3.64±0.09 mmol/L. All parameters returned to the normal values with 24 h after operation.

**Intraoperative monitoring**

In all cases, a clear positive effect was observed: suprasellar elevation of the tumor capsule occurred, which provided conditions for full examination of all portions of the sella cavity and removal of tumor remnants.

In all cases, the hypotensive effect retained throughout operation, and there was no need for an additional decrease in CSF pressure by lumbar CSF outflow into a drainage, which remained closed until the end of surgery.

Intraoperative liquorhea occurred in 5 (5.95%) surgeries, but it was successfully stopped.

**Postoperative monitoring**

None of the patients displayed signs of postoperative liquorhea or postoperative meningitis. Postoperative signs of hypocorticoidism associated with replacement therapy were observed in 1 patient only; hypocorticoidism was treated by increasing doses of hormonal drugs. All patients were discharged from the clinic in satisfactory condition within the standard period of time (5—8 days).

**Conclusion**

The study demonstrated that persistent intracranial hypotension during transnasal surgery can be provided by a non-invasive method. Laboratory tests demonstrated the safety of the method for the patient’s homeostasis system. The HyperHAES plasma substitute medicine (a hypertonic iso-oncotic solution) rendered unnecessary the use of a potentially risky external lumbar drainage in ordinary transnasal surgeries that are associated with a low risk of large skull base defects and constitute the bulk of surgeries performed at the clinic.

In cases where the risk of a significant skull base defect and the need for multi-layer plastic surgery is high (e.g., in the case of extensive approaches), the use of an external lumbar drainage is reasonable and has no alternative so far.

**REFERENCES**


Commentary

Introduction of the endoscopic transsphenoidal technique for resection of tumors in the chiasmosellar region opened up new horizons in neurosurgical treatment of mass lesions of the aforementioned localization, particularly, pituitary adenomas. This led to a significant increase in the number of transsphenoidal surgeries, reduction in the injury rate, and increase in the radicalness and safety of these operations. However, a number of certain difficulties in performing these operations remain; one of them is hindered visualization of the resected tumor bed during bringing down the diaphragm and the superior part of the tumor capsule in the case of its suprasellar spread. One of the key techniques used to return the capsule to its “original” position was lowering of intracranial pressure (ICP) by placement of a lumbar drainage to remove a required amount of CSF. The technique worked well for many years of neurosurgical practice; however, like all invasive techniques, it has several disadvantages, including liquor-dynamic and dislocation complications, infectious complications, pneumocephalus, changes in the CSF composition, post-puncture syndrome, hemorrhagic complications, and direct injury.

The group of authors from the Burdenko Neurosurgical Institute used intravenous infusion of a HyperHAES solution (Fresenius Kabi, Germany), a 7.2% NaCl solution in 6% HES 200/0.5, in a sufficiently large group of patients and achieved good results in terms of ICP regulation; actually, they used it as an alternative to the previously used method. The study demonstrated almost complete safety of the approach, which required only monitoring of the patient’s homeostasis for 24 hours.

In my view, the emergence of this non-invasive technique of lowering intracranial pressure, coupled with secondary procedures (if necessary), such as temporary anesthesia in a hyperventilation mode or moving of a patient into the semi-sitting position, can provide a good substitute for the method routinely used to reduce ICP, lumbar drainage, in endoscopic surgery for tumors with suprasellar spread. At the same time, I would recommend the authors to continue further research and develop an algorithm for unambiguous establishing of the indications for which placement of a lumbar drainage is still required or highly desirable.

A.Yu. Grigor’ev (Moscow, Russia)
Multiple Primary Liponeurocytoma of the Central Nervous System


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We report a unique case of multiple primary liponeurocytoma. Liponeurocytoma is a rare benign tumor (Grade II) of the posterior cranial fossa (PCF) that is composed of neural, probably astrocyte, lineage cells; the tumor stroma contains mature adipocytes. There are only 37 cases of cerebellar liponeurocytoma described in the literature. Up to now, no case of multiple primary liponeurocytoma with extracranial and intracranial nodes has been reported.

Liponeurocytoma was first described in the literature in 1978. J. Bechtel et al. [1] presented a case of a patient with a cerebellar hemisphere tumor. Histological analysis of the tumor specimen revealed mature adipocytes as well as areas typical of medulloblastoma, astrocytoma, ependymoma, and oligodendroglioma. Despite heterogeneity of the morphological picture, liponeurocytomas have a low proliferative activity.

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The distinctive feature of this tumor type is a relatively benign clinical course and favorable prognosis for the disease. Until the early 2000s [2], this type of tumors was referred to as lipomatous medulloblastoma, lipomatous glioneurocytoma, etc. [3—5]. Given the histological, morphological, and immunohistochemical features of this tumor type, the 2000 WHO classification [6] recognized it as a nosological entity in the group of neuronal tumors. The 2007 WHO classification of nervous system tumors refers cerebellar liponeurocytoma to WHO Grade II benign tumors [7].

This article presents a rare case of a patient with multiple primary liponeurocytoma of the CNS.

Case Report

A 49-year-old male patient M. was admitted to the Burdenko Neurosurgical Institute in 2005. He complained of cervical spine pain and sensory disturbances in both hands. Objective examination revealed hypesthesis and mild cerebellar symptoms. Magnetic resonance imaging (MRI) of the brain and all segments of the spinal cord detected 3 tumor nodes: a PCF tumor causing the neurological symptoms and 2 intradural extramedullary nodes at the C6 and L5—S1 levels. It is worth noting that the two extramedullary nodes were asymptomatic, and the decision on the subsequent treatment strategy for these entities was made after histological examination of the PCF tumor. On the basis of the obtained results, it was decided to perform surgical treatment of the PCF tumor (Fig. 1).

T1-weighted MRI without contrast enhancement (a) and turbo inversion recovery magnitude (TIRM) MRI (b) scans revealed a large space-occupying lesion in the inferior cerebellar vermis region that had a heterogenous structure with extensive areas of a hyperintense MRI signal whose intensities were identical to that of adipose tissue of the occipital region. The lesion extended to the spinal canal up to the C2 level (mostly to the right) through the foramen of Luschka of the fourth ventricle (the tumor node is indicated by the arrow).

The patient underwent resection of a tumor of the fourth cerebral ventricle and the cisterna magna on February 24, 2005. During surgery, the tumor was noted to have the exophytic growth pattern and spread rostrally under the dura mater. The lesion had macroscopic similarity to ependymoma and was also diagnosed as ependymoma by emergency biopsy. Total resection of the lesion was performed, mainly with the use of an ultrasonic destructor. The tumor was adherent only to the vascular plexus region of the median aperture on the left side. After tumor resection, almost all parts of the fourth ventricle could be visualized. The ventricle floor looked normal.

On the basis of a final pathomorphological examination using immunohistochemical analysis, the tumor was diagnosed as liponeurocytoma with positive expression of GFAP (glial fibrillary acidic protein) and Syn in tumor cells. Foci of mature adipocyte clusters with the Ki-67 labeling index under 5% were detected.

The patient withstood the surgery well and was discharged without worsening of the neurological symptoms on the 7th day after surgery.

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In 2008, control MRI revealed an intracranial tumor recurrence and progressive growth of the extramedullary tumors, but no worsening of the neurological symptoms was detected. Therefore, a course of radiation therapy to the removed tumor area was performed using a Primus linear accelerator according to a hyperfractionation scheme: 2 Gy was delivered in 18 fractions with 6 static fields. Intradural nodes at the cervical and lumbosacral spine levels were exposed to radiation using a Novalis linear accelerator. Twelve fractions of 1.8 Gy were delivered to each of 2 foci (bust) using 3 and 4 dynamic arcs, respectively.

The patient was followed-up by contrast-enhanced MRI for 3 years. According to MRI, growth of the PCF tumor and the node at the cervical level was stabilized, and size of the tumor at the L5—S1 level slightly decreased.

Follow-up was discontinued for some time due to satisfactory condition of the patient. However, an aggravation of pain in the lumbar spine, urinary problems, and decreased sensitivity in the perineum developed in the patient in April 2013 (Fig. 2).

Examination findings (2013). T1-weighted contrast-enhanced MRI (see Fig. 2a) revealed a mass lesion with a hyperintense area (due to adipose tissue) in the fourth ventricle region, caudal parts of the cerebral aqueduct, and anterior parts of the third ventricle. The tumor moderately accumulated a contrast agent.

Computed tomography (CT) at the PCF level without contrast enhancement (see Fig. 2b) and after intravenous contrast administration (see Fig. 2c) revealed a mass lesion in the fourth ventricle projection with areas of a hypointense signal (fat tissue). A mass lesion accumulating a contrast agent was seen in the left cerebellopontine angle (tumor node is indicated by the arrow) (see Fig. 2c).

The CBW map of CT perfusion (see Fig. 2d) revealed the identical digital indicators of tumor blood flow in tumor nodes in the fourth ventricle and left cerebellopontine angle projection; tumor blood flow was moderately increased compared to that of the brain substance. Examination of the whole longitudinal axis of the spinal cord revealed multiple neoplastic lesions of the intradural extramedullary localization at the C6 (see Fig. 2e) (tumor node is indicated by the arrow) and L5—S2 levels (see Fig. 2f). The tumor node at the L5—S2 level had a low intensity signal in T2 (see Fig. 2f) and T1 (see Fig. 2g) modes, with local areas of an increased signal in the T1 mode (fat tissue). After intravenous injection of a contrast agent, its heterogeneous uptake was detected in the tumor structure (see Fig. 2h).

On September 03, 2013, the patient underwent surgical removal of an intradural tumor at the L4—S2 level.

During surgery, a gray-pink tumor was identified. It had no sac and was tightly adjoining to the cauda equina roots. The tumor node spread through the thinned and fenestrated dura mater into the spinal canal and macroscopically resembled ependymoma. In this case, the visualized terminal filament was included in the tumor stroma, but it was not an origin of initial tumor growth. The granular and loose structure of the tumor prevented its en bloc resection, so the bulk of the tumor was removed using an ultrasonic aspirator. After tumor removal, the patient continued to undergo a course of radiation therapy to the removed tumor area.
removal, the intradural space was cleared; distinctive cerebrospinal fluid pulsation appeared; and the roots were loosely arranged. The neurological symptoms partially regressed, and the patient was discharged on the 10th day after the surgery.

Further, the patient was followed-up at the Department of Radiology of the Burdenko Neurosurgical Institute. It was decided to irradiate the residual tumor mass at the L4—S2 level to prevent continued tumor growth.

On March 24, 2014, stereotactic radiosurgery was performed in the resected tumor bed area at the L4—S2 level using a CyberKnife robotic linear accelerator. 10 Gy was delivered to the 81% isodose (118 beams; 7 mm collimator). The patient withstood irradiation well.

However, according to the MRI data of the brain performed in March 2014, continued tumor growth in the area of the inferior cerebellar vermis and cerebellar tonsils was detected; the lower tumor pole descended to the C3 level (Fig. 3).

On April 30, 2014, a recurrent liponeurocytoma of the fourth ventricle was resected. A gray-yellow colored tumor was associated with the ependyma of the fourth ventricle floor. During tumor mobilization, a sharp response of the caudal nerve group associated with a short-term cardiac arrest was observed. The cardiac function was restored by emergency massage. The tumor node was resected almost completely. The second tumor node was located anteriorly to the striae medullaris. It was tightly adjoining to the fourth ventricle floor in the projection area of the facial nerves. The most part of the tumor was removed using an ultrasonic aspirator. After removal of the liponeurocytoma, clear responses of both facial nerves were evoked.

The patient was discharged on the 12th day after the surgery. Diplopia and ataxic gait were observed in the patient’s neurological status.

Significant deterioration in the patient’s condition occurred soon after discharge, including increasing ataxia, disorientation and confusion episodes, and daily headache. Because of worsening of the neurological symptoms, the patient underwent MRI on May 06, 2014. The MRI data revealed triventricular hydrocephalus, residual tumor fragments in the Sylvian aqueduct area, tumor spread into the third ventricle, and signs of obstruction of cerebrospinal fluid flow at two levels. After the examination, expectant treatment of the patient was approved. The progression of hydrocephalus was detected on the control MRI scans (June 02, 2014). In this regard, ventriculoperitoneal shunting, septostomy, and stenting of the right foramen of Monro were performed. The treatment led to a partial regression of the disorders, but the gross oculomotor brainstem symptoms at the level of the horizontal gaze center with signs of internuclear ophthalmoplegia and moderate ataxia still remained.

Discussion

Cerebellar liponeurocytoma is a rare tumor comprised of neuronal, probably astrocyte, lineage cells with a low proliferation rate, which leads to a favorable clinical prognosis [2, 6].

Only one case of cerebellar liponeurocytoma metastasis after tumor resection was reported. In our clinical case, we cannot exclude the possibility of tumor implantation through the meninges and cerebrospinal fluid pathways. However, at the follow-up beginning, as many as three tumor nodes were detected in the patient...
### Review of world experience in the treatment of liponeurocytoma

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### Diagnosis

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Footnote: LNC — liponeurocytoma; LCH — left cerebellar hemisphere; RCH — right cerebellar hemisphere; CPA — cerebellopontine angle; TR — total resection; SR — subtotal resection; RT — radiation therapy; IORT — intraoperative radiation therapy.
(two of them were operated on) that were followed up for 10 years. Therefore, this unusual phenomenon can be regarded clinically as a multiple primary tumor.

The tumors in the PCF and at the C6 and L5—S1 levels were detected as early as in 2005. A case of cerebellar liponeurocytoma metastasis was found in the available literature [11], but no references to a multiple primary process were found. There is a description of aggressive tumor behavior associated with invasion into the meninges and morphological signs of malignancy (high proliferative rate and cellular atypia) [12].

According to the cerebellar lesion biopsy after the first surgery performed in 2005, the tumor consisted of relatively small cells with pale cytoplasm and round, clear-cut nuclei. The cell density was moderate; polymorphism, mitotic figures, and necrotic changes were absent. In addition, focal adipocyte clusters were detected (Fig. 4). Immunohistochemical analysis of the tumor cells revealed clear positive expression of synaptophysin, focal expression of GFAP, and a low (less than 5%) labeling index of the MIB1 marker (Ki-67). The morphology and immunophenotype of the tumor were consistent with the diagnosis of cerebellar liponeurocytoma.

A similar morphological pattern was also found in the bioplate of the intradural tumor at the L5—S2 level (2013): the tumor had a biphasic structure and consisted of small round cells with clear-cut nuclei and foci of tightly adjacent adipocyte clusters. Immunohistochemical analysis revealed that the tumor cells were positive for synaptophysin and GFAP; the Ki-67 labeling index of the proliferation marker MIB1 amounted to 5—7%, which was slightly higher than that of the cerebellar tumor found in 2005. The tumor cells were negative for epithelial markers (AE1/3, CK7, CK20) as well as for PLAP, CD117, Des, and smooth muscle actin. The final histological diagnosis was liponeurocytoma.

Histological and immunohistochemical studies of the biopsy of the surgery material (April 2014) confirmed the diagnosis of liponeurocytoma. The distinctive feature of this liponeurocytoma compared to the previous tumors was an elevated (up to 7—8%) proliferative potential of the Ki-67 labeling index and mitotic figures, which were rather common in the tumor cells.

Analyzing the patient’s disease dynamics for the period from 2005 to 2013, we can state a fact that the tumor is sensitive to the high-dose radiation therapy.

We analyzed international experience in treatment of 37 patients with the diagnosis of liponeurocytoma (see Table).

All 37 patients underwent surgical treatment. Of them, 24 had total tumor resection, and 13 underwent subtotal resection, or there was no information on the tumor resection extent. Two patients died in the early postoperative period. One patient died 19 months after tumor resection on the background of continued tumor growth. Another patient had two reoperations for recurrent tumor and died after 11 years of follow-up on the background of a new tumor recurrence. One patient had liponeurocytoma metastases [11].

Out of the operated patients, 15 patients underwent additional radiation therapy. Of them, prior to radiation exposure, 13 patients underwent total tumor resection, and 2 patients had subtotal resection. Among patients of this group, only one patient was diagnosed with continued tumor growth. It should be noted that this patient received a course of radiation therapy after total tumor resection and had the proliferation tumor index of less than 3%.

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**Fig. 3.** a — T2-weighted MRI of the brain, b — contrast-enhanced T1-weighted MRI of the brain.
Out of 18 patients who did not receive radiation therapy in the postoperative period, recurrent tumor was observed in 6 cases. Given a limited amount of the data and slow tumor growth, the conducted analysis does not allow us to determine reliably the factors affecting the relapse rate and the effect of alternative therapies on the survival rate or duration of the recurrence-free period. However, given this shallow analysis, radiation therapy seems to extend the asymptomatic stage and affect qualitatively the relapse rate.

**Conclusion**

Cerebellar liponeurocytoma is a rare benign WHO Grade II tumor. No specific CT and MRI signs of liponeurocytoma have been described so far. Therefore, we tried to focus on diagnosis of this tumor and its distinctive features using modern neuroimaging techniques (MRI and CT perfusion in various modes). Given an example of one clinical case, we are not in the position to recommend the exact treatment tactics, which is to a greater extent determined by the clinical signs and patient condition. Perhaps, given slow tumor growth and rare malignancy of liponeurocytoma, the most optimal tactics of patient management is combined treatment that includes radical tumor resection and subsequent radiation therapy, which may be supplemented with symptomatic treatment, depending on the patient condition.

*Fig. 4. Histologic specimen of the tumor.*

a — focus of increased proliferative activity ($\times400$). Immunohistochemical expression of Ki-67 marker; b — mitotic figures in tumor cells ($\times400$); c — general appearance of liponeurocytoma, which is predominantly composed of round-shaped tumor cells, small amount of adipocytes ($\times200$). Hematoxylin and eosin staining.
REFERENCES


Commentary

The authors were the first in the world to describe a case of primary multiple liponeurocytoma of the CNS. Liponeurocytoma of the CNS is extremely rare tumor pathology: only 37 cases of single liponeurocytoma of the CNS have been described in the world literature until the present time, whereas this article presents a case of a single multiple liponeurocytoma with one intracranial and two extracranial intradural extramedullary nodes.

The clinical case is presented by a 49-year-old patient admitted to the Burdenko Neurosurgical Institute in 2005. The patient complained of cervical pain and sensory disorders in both hands. Neurological examination of the patient revealed cerebellar symptoms and hypoesthesia of both hands. MRI scans of the head and spine showed 3 tumor nodes: one tumor of low regions of the cerebellar vermis and the fourth ventricle, which caused neurological symptoms according to the authors’ point of view, and two intradural extramedullary nodes at the C6 and L5—S1 levels. Unfortunately, the authors did not provide images of spinal lesions. The assertion that the spinal nodes were asymptomatic does not seem quite logical, since the patient had complained of cervical pain and numbness in the hands, which revealed hypoesthesia. However, the decision to start treatment for PCF tumor seems to be absolutely correct.

On 24 February 2005, the tumor of the cerebellar vermis and the fourth ventricle was resected; follow-up was scheduled after histological verification. It is not quite clear who was responsible for the decision, i.e. whether the patient was discussed at a council of radiologists and chemotherapists, and whether the literature was analyzed in 2005. It is also unclear how exactly the follow-up was performed. It was only noted that the MRI performed in 2008 had revealed the progression of the disease, namely a relapse in the area of the removed tumor (the cerebellar vermis and the fourth ventricle) and the growth of spinal structures without worsening of clinical symptoms. The remote gamma-therapy was subsequently performed for tumor nodes and was accompanied with follow-up for 3 years. The follow-up period was perhaps insufficient, causing undetected in time tumor progression and the development of persistent neurological deficits.

The analysis of world literature has revealed no definite algorithm for treatment of patients with this rare disease, but the authors have rightly acknowledged a tendency to a significant improvement of treatment outcomes when radiation techniques are included in the combined treatment. The use of radiation therapy in the early stages could probably contribute to a more favorable prognosis for the disease.

This rare and very interesting clinical case is a good reason for a practical conclusion: the treatment tactics for patients with malignant and rare tumors should be developed collectively, i.e. during a council of neurosurgeons, oncologists, radiologists, and chemotherapists.

A.M. Zaytsev (Moscow, Russia)
3. Treatment of patients with acute spine and spinal cord injuries

3.1. Prehospital emergency first aid for patients with suspected spinal injuries

In order to provide qualified prehospital management of patients with suspected spine and spinal cord injuries (SCI), the following conditions should be fulfilled:

1. Each emergency team (ET) should be equipped with a hard cervical collar, methylprednisolone, and a stretcher or a vacuum mattress (an option).

2. Any patient with a suspected SCI, including unconscious patients, after a road traffic accident (RTA), fall from a height, diving into shallow water, or beating must be immobilized at the scene of an accident and during transfer (an option). The best immobilization method is believed to be the application of a hard cervical collar and a rigid board under patient’s back and securing the patient with straps. The combination of a hard cervical collar and a vacuum mattress may be an option. Patient’s spine should be considered damaged until proven otherwise.

3. At the scene of an accident before and during transfer to the hospital, the patient’s head should be immobilized using a hard cervical collar, methylprednisolone, and a stretcher or a vacuum mattress (an option).

4. In suspected thoracic or lumbar spine injury, the patient should be transferred using a hard backboard. Such patients should be lifted by 3 or 4 men, who should put their hands under all parts of the patient’s spine and perform these activities without jerking.

5. Gentle and fast transportation of the SCI patient to the nearest multidisciplinary hospital is required. The hospital should afford to admit and manage patients with severe polytrauma day and night, to include a neurosurgical or spinal department, and to provide high-technology equipped neurosurgical care and specialists certified in newest spinal surgery technologies.

6. The hard cervical collar provided by an emergency team should be replaced by another cervical collar at hospital after lifting the patient on a gurney in the admission department or on the bed in the intensive care unit.

3.2. Management at hospital

3.2.1. Treatment of patients with acute SCI

SCI patients should be treated at a hospital endowed with the following equipment: operating room with a multifunctional X-ray transparent surgical table; image intensifier, preferably capable of providing 3D reconstruction of the spine; set of microsurgical instruments; high-speed drill; Kerrison pliers and conchotomes; microscope or binocular loupes; systems for plate and laminar screw fixation of the cervical spine; halo devices; pedicle screws, and anterior plates for thoracic and lumbar spine fixation.

Keywords: traumatic injury, spine, spinal cord.
The main objectives of surgical treatment for patients with SCI are as follows:
1. Early complete decompression of the spinal cord and other neurovascular structures of the spinal canal;
2. Three-dimensional restoration of the spinal axis;
3. Fixation and stabilization of the spinal column aimed at patient’s early immobilization; acceleration of callus formation; prevention of the progression of neurological symptoms, late deformities, and pain syndrome.

3.2.2. Indications and contraindications for surgical treatment of patients with SCI

Indications for emergency surgery
1. Onset and/or progression of spinal neurological symptoms, which is typical of early compression not followed by spinal shock.
2. Deformation of the spinal canal by radiopaque (bone fragments, structures of dislocated vertebrae, or due to severe angular deformity: over 11°, 40°, and 25° in the cervical, thoracic, and lumbar spine, respectively) or radiolucent (hematoma, traumatic spinal disc herniation, damaged ligamentum flavum, or a foreign body) compressing compounds.
3. Insulated hematomyelia combined with obstruction of the cerebrospinal fluid pathways.
4. Clinical and angiographic signs of vascular embarrassment of the great vessel of the spinal cord (immediate surgical intervention is indicated!).
5. Hyperalgic and paralytic spinal nerve root compression.
6. Unstable injuries to the vertebral motor segments, which can cause dislocation of a vertebra or its fragments and secondary spinal cord compression.
7. The presence of foreign bodies in the spine or their immediate proximity to the spine.
8. Liquorrhea.
9. Complicated injury with a damage to the dura mater (DM) (in case of stab and gunshot spinal wounds).

Contraindications for surgical treatment in patients with acute SCI:
1. Traumatic or hemorrhagic shock with hemodynamic instability;
2. Concomitant internal organ damage (internal bleeding; the risk of peritonitis; myocardial contusion with signs of impaired cardiac function, or multiple injuries of ribs followed by hemopneumothorax and signs of respiratory compromise: SO₂ level during insufflation of oxygen of less than 85%).
3. Severe brain injury accompanied by loss of consciousness (the Glasgow Coma Scale score less than 10 or 11) in suspected intracranial hemorrhage.
4. Severe concomitant diseases, accompanied by anemia (hemoglobin level of less than 80—90 g/L), cardiovascular collapse, and renal (anuria or oliguria; urea level of more than 20 mmol/L, creatinine level of more than 180 mmol/L) and/or hepatic (the total protein content of more than 50 g/L, increased enzyme activity by more than 3—4 times) insufficiency.
5. Systemic fat embolism, pulmonary embolism (PE), pneumonia, or unfixed limb fractures (for surgeries using the posterior approaches).
6. Gunshot or blast-induced injury to the spinal cord at the C1—C4 level with the clinical presentation of a total loss of function of the spinal cord.

3.2.3. Treatment of SCI patients with the absence of bone trauma

External fixation of the spine is required until the stability of the injury is confirmed via functional tests (flexion, extension, and axial traction) under doctor’s supervision. Rigid external immobilization performed by applying a cervical collar at the level of spinal cord injury for more than 12 weeks is of no use. It is unreasonable to restrict the activity of such a patient for more than 6 months after injury (an option).

3.2.4. Treatment of patients with acute SCI in the intensive care unit

Preparation of a patient for surgery
1. All patients with acute, either complicated or uncomplicated multilevel cervical spine or thoracic spine (up to the T7 level) injuries, as well as patients with SCI and polytrauma should be admitted to an intensive care unit. Monitoring of cardiac function and respiratory activity is obligatory for timely diagnosis of cardiovascular and respiratory diseases (an option).
2. It is necessary to maintain the mean arterial blood pressure at the level of 85—90 mmHg during the first week after acute injury to improve the spinal cord perfusion pressure. If hypotension is detected (systolic pressure of less than 90 mmHg), it is essential to normalize blood pressure as soon as possible (an option).
3. Methylprednisolone treatment (5.4 mg/kg per hour) in the first 24 hours (providing that the treatment is initiated within the first 8 hours) is at doctor’s discretion due to a high risk of side effects (e.g., gastrointestinal hemorrhage). GM-1 ganglioside administration is advisable (an option).
4. Surgical treatment of patients with compression of the neurovascular structures of the spinal canal in the absence of contraindications for surgery should be performed as early as possible, since 70% of all irreversible ischemic changes, which are arising from compression of the brain and cerebral vessels, occur within the first 4—8 hours. Therefore, the existing surgical contraindications should be actively managed in the intensive care unit as soon as possible.
5. Background therapy includes regulation of respiratory and cardiovascular functions; control over the biochemical indices of homeostasis; cerebral edema control; measures for preventing infectious complications, decubitus ulcers, hypovolemia, and
hypoproteinemia; regulation of the pelvic function by either inserting the Monroe tidal drainage or by bladder catheterization at least 5 times a day; management of microcirculatory disorders; normalization of rheological properties of blood; administration of antihypoxic, vasoprotective, cytotoxic agents, etc.

6. Relative hypovolemia, which is typical of patients with SCI, may be the cause of postural collapse and sudden cardiac arrest. Therefore, these patients require replacement of the circulating blood volume under the control of central venous pressure and plasma osmolality (range of 280—310 mOsm/L) especially in case of hyperglycemia, renal insufficiency, uncontrolled administration of osmotic diuretics and saluretics, and under alcoholic intoxication.

3.2.5. Treatment of patients with SCI of the upper cervical spine (C1—C2)

At the “treatment at hospital” stage patients with SCI of the upper cervical spine should be managed in specialized spinal centers by physicians experienced in treating this disease.

Early repositioning with craniocervical traction is recommended for patients with an atlanto-occipital dislocation. The method of choice for this type of dislocation is halo traction and internal fixation (occipital cervical fusion) using the newest implants for stable fixation of the upper cervical spine, which employs one or two stages. Traction in patients with an atlanto-occipital dislocation is associated with the 10% risk of neurological complications (an option).

An isolated fracture of the atlas with no rupture of the transverse ligament requires external fixation only, whereas in case of ligament rupture (in atlanto-occipital dislocations), external fixation or occipital cervical fusion is needed (an option). C1 fracture (Jefferson fracture) requires either halo fixation or occipital cervical fusion (an option) (see Appendix 3 in issue #6, 2014).

Anterior transligamentous, transodontoid, and posterior transodontoid atlas dislocations in acute injury can be restored in one of two ways: (1) skeletal traction or (2) open (surgical) repositioning. After the atlas dislocation is restored, either atlantoaxial spinal fusion is performed or external fixation using a halo device, an orthopedic corset, or a thoracocranial plaster cast for 10—12 months is applied. Spinal cord compression requires either decompressive laminectomy and posterior occipital cervical fusion or external fixation for 3 to 6 months (an option).

External fixation for a month is indicated in patients with type I odontoid process fracture (an option).

In odontoid process fracture of type II or type III, patients older than 50 years require surgical treatment (transodontoid fixation with one or two cannulated screws, halo fixation, or posterior atlanto-axial fusion using either the Magerl’s technique or hooks and a bone graft) (recommended). Patients younger than 50 years can be initially treated using rigid external immobilization for 3 to 6 months (an option).

Surgical treatment of patients with type II and III fractures of the odontoid process is required for the odontoid process displaced by over 5 mm, for fragmentation of the odontoid process fracture (type II A), and/or for the inability to achieve or maintain repositioning via external immobilization (an option). The use of the halo device, as well as repositioning and fixation (either C1—C3 transpedicular fixation or C1—C3 fixation using hooks and a bone graft for spinal fusion, or the combined fusion using transpedicular screws, hooks, and a bone graft) are indicated.

C2 open repositioning, C2—C3 discectomy, and anterior spine fusion (optimally, using a bone/cage and a titanium plate) are performed in case of C2 dislocation accompanied by disk rupture. If posterior structures are also damaged, posterior fixation is also required (an option). External fixation is possible for C2 isolated undisplaced vertebral body fractures (an option).

Treatment of patients with combined atlantoaxial fractures is based on the features of a C2 fracture. External fixation is indicated for most C1—C2 fractures. The combination of C1 fracture and type II C2 fracture with an atlantodental interval of 5 mm or more, as well as the combination of C1 and C2 hangman’s fractures with C2—C3 angulation of 11° or more require one of the three following surgical options:

1. Open anterior repositioning of C2 and anterior spine fusion of C2—C3 using a bone autograft/allograft or probably a cage, either with or without additional plate fixation. The treatment is combined with halo device immobilization or external fixation in the postoperative period;
2. Occipital cervical fusion;
3. Combined anterior and posterior spine fusion.

Occipital cervical fusion is indicated in case of significant C1 fragmentation followed by inability of using a halo device to restore the ring of the atlas (an option).

3.2.6. Treatment of patients with injuries of the cervical spine and spinal cord at the C3—C7 level (fractures)

In uncomplicated injury (an option)

Unstable fractures of vertebral bodies require corpectomy of the ruptured vertebra(e) and anterior spine fusion with a bone autograft or allograft and a cervical titanium plate. Removal of discs adjacent to the broken vertebra, their subsequent replacement by bone grafts, and plate fixation are possible in a number of cases in the absence of compression of the spinal cord and its roots by bone fragments. For fractures of the posterior portions of vertebrae followed by penetration of bone fragments into the spinal cord lumen and compression of the spinal cord or its roots, the removal of the invaded fragment from the spinal canal is indicated. Only an
unstable injury requires posterior spine fusion using a system with laminar hooks or screws either for transpedicular fixation or for their placement into the lateral masses.

External fixation for 1.5 months is required (as option) for patients with isolated fractures of vertebral arches or articular process.

In complex injury (an option):
1. Vertebral compression fractures require anterior decompression and spinal fusion with fixation (fusion using a bone autograft and a plate);
2. Fractures of posterior structures require posterior decompression and fixation (transpedicular screw fixation, lateral mass screw fixation, or a laminar system);
3. In the case when all the three grey columns are damaged, anterior decompression and stabilization (spinal fusion with a bone autograft and a cervical plate) are required;
4. In the case when more than two (adjacent) vertebrae are damaged, anterior decompression, fusion with a bone autograft/allograft and a plate, and posterior fixation (either transpedicular one or fixation through lateral masses, or fixation using a laminar system) are required. In some cases, anterior decompression and spinal fusion with a bone and a plate alone are sufficient.

3.2.7. Treatment of patients with dislocations of the cervical spine at the C3—C7 level

Repositioning and stabilization of vertebrae are required as early as possible: the removal of a ruptured disc, open reduction of a dislocated vertebra, and spinal fusion using a bone autograft (or a cage with bone crumbs or allograft/xenograft) and cervical titanium plate (an option).

According to the magnetic resonance imaging (MRI) data, the absence of disc herniation at the dislocation level in some cases enables open posterior repositioning and fusion (fusion with screw placement into lateral masses, using a transpedicular screw system or laminar hooks) (an option).

Treatment with the long-term traction in bed is possible when newer methods of treatment are not available or if the patient is in severe condition and there is no traumatic disc herniation in the spinal canal lumen (according to MRI data, disc herniation occurs in a third of patients). After applying skeletal traction by parietal tubers, subsequent correction of head position, traction weight correction, and X-ray control are required. After the repositioning of dislocation and stabilizing the patient’s condition, he or she undergoes the surgery: removal of a ruptured disc and anterior fusion with a bone autograft (or a cage with bone crumbs or allograft) and cervical titanium plate (an option).

3.2.8. Treatment of patients with a vertebral artery injury following the penetrating cervical trauma

Intravenous anticoagulant injection is required for patients with injured vertebral artery with the clinical presentation of ischemic stroke involving the posterior cerebral artery circulation, (an option).

Medical supervision and anticoagulant therapy are indicated as an option for symptoms of vertebrobasilar insufficiency due to vertebral artery injury.

In case of the vertebral artery injury with no clinical presentations, three-month follow-up is indicated (an option).

3.2.9. Management of patients with SCI of the thoracic and lumbar spine

1. In the absence of neurological deficit

Stable compression fractures of the thoracic and lumbar vertebral bodies of types A1 and A2 (especially multiple injuries) with kyphosis of more than 25° (but no more than 40°) for the thoracic spine and over 10—15° for the lumbar spine with no spinal cord compression may be treated either by single-stage closed reclination using a swab or by the use of various reclination devices. Bed rest for 24 weeks and thoracolumbosacral external fixation for a term of 1 to 3 months are recommended. Control MRI should be performed after 3, 6, and 12 months to eliminate the increasing kyphosis and late spinal cord compression. Alternatively, vertebroplasty, kyphoplasty, and vertebral body stenting may be used, especially in patients with osteoporosis. In the case of A2 type vertebral fractures and vertebral height loss (≥50°), indicated is as follows: either a) anterior reclamation using traction systems (vertebral body prostheses) and fusion with a bone autograft and a titanium plate or anterior rod-based system or b) posterior transpedicular fusion with reclamation of a broken vertebra, which is possibly combined with kyphoplasty (within the first 3 to 7 days in the young and 3 to 12 days in elderly patients).

Unstable cord injury. Uncomplicated (type E) or low complicated (type D, ASIA) unstable compression fractures of the thoracic and lumbar spine (types A2 and A3, respectively) require either anterior reclamation (preferably with the use of traction systems, i.e. a vertebral body prosthesis) or anterior spine fusion (using either a bone autograft/allograft and a plate or an anterior rod-based system). In the presence of fracture fragments or fragments of an intervertebral disc in the spinal canal, anterior decompression is required. A3.2 fractures require bisegmental posterior transpedicular fusion with single-stage reclamation of a broken vertebra.

Uncomplicated (type E) or low complicated (type D, ASIA) unstable distraction fractures (B1, B2, and B3 types) should be corrected either with percutaneous/open transpedicular fusion or posterior stabilization using hooks or hybrid systems (with pedicle screws and hooks). In the case of destruction of the anterior grey column, the surgery is accomplished with anterior fusion.
using, where possible, video assistance or special retractors for minimally invasive approaches. Bed rest within 1 to 3 days and thoracolumbosacral orthosis for 1—3 months are recommended.

In uncomplicated (type E) or low complicated (type D, ASIA) unstable rotation injuries of the thoracic or lumbar spine (type C), anterior open reduction and internal fixation (transpedicular, laminar, or hybrid) must be applied, whereas the compression of the spinal canal structures requires decompression; the anterior fusion should be performed subsequently: either simultaneously or after some time.

2. With neurological deficit

Stable cord injury. Laminectomy and spinal cord revision with local hypothermia are recommended (an option). In the presence of kyphosis they are combined with reclamation and posterior stabilization using hooks, pedicle screws, or hybrid (pedicle screws and hooks) systems. Bed rest within 1 to 3 days and thoracolumbosacral orthosis for 1—3 months are required.

Unstable cord injury. Laminectomy (or laminectomy and extended unilateral costotransversectomy) with anterior transpedicular decompression of the spinal canal, spinal cord revision, local hypothermia to the spinal cord (an option), open reclamation and/or repositioning, and posterior fusion (using either pedicle screws or hooks, or a hybrid system [pedicle screws and hooks]) are indicated. Anterior fusion using a bone graft, vertebral body prosthesis, and possibly a plate and/or an anterior rod-based system is either single-stage fusion or is performed 2—3 weeks after the patient’s condition was stabilized. Bed rest within 1 to 3 days and thoracolumbosacral orthosis for 1—2 months are required.

An unstable vertebral fracture at the L5 level (A2, A3, B1—B3, and C1—C3 fractures) requires transpedicular fusion of L3—L4—S1, which is accompanied by minimally invasive anterior fusion of L4—S1 using a traction prosthesis of the vertebral body and a bone autograft in case of destruction of the L5 vertebral body. If there is possibility to save the L5 vertebral body, the L4—L5 and L5—S1 discs should be removed and replaced by bone grafts. During fusion, it is unreasonable to use an isolated bone graft or meshes without endplates due to a high risk of spinal fusion inefficiency, breakage of a bone graft, endplates of the adjacent vertebrae to be cut by a mesh, increasing kyphosis, and screw breakage.

Note. All patients with concurrent osteoporosis require anterior or posterior fixation with cannulated screws and single-stage vertebroplasty through these screws.

All patients should undergo posterior transpedicular fusion possibly using minimal invasive techniques (e.g., percutaneous fixation).

If special equipment is available, it is advisable to perform anterior fusion either endoscopically or using minithoracotomy and endoscopic assistance.

Patients with a severe combined injury are recommended to undergo surgical correction and stabilization of the spine with percutaneous/conventional pedicle screw, hook, or hybrid (screw and hook) systems, and posterior fusion within the first 72 hours. Under indications for anterior spine fusion, the surgery can be performed 1—2 weeks after the complete patient’s stabilization (up to moderately severe or satisfactory condition) and compensation of functions of the basic life support systems.

In the case of isolated SCI, either one-stage or two-stage surgical treatment via anterior, posterior, or combined (anterior and posterior) approaches are possible.

3.2.10. Therapeutic approach for patients with stab, gunshot, and blast wounds of the spine

The therapeutic approach includes the following procedures:

— careful initial surgical debridement of the wound entry and exit holes;
— removal of foreign bodies; collection of specimens from the wound and foreign bodies for culture and antibiotic sensitivity test;
— meningomyeloradiculitis;
— restoration of the spinal canal lumen and the continuity of DM;
— spine stabilization for the unstable injury;
— drainage for the passive outflow through counter-aperture incision in the case of wound contamination and possible liquorhea;
— lumbar drainage up to 2—5 days in the postoperative period (depending on inflammatory response) for injured DM;
— prescription of broad-spectrum antibiotic therapy combined with anaerobic infection prophylaxis from the very first minutes after admission;
— hyperbaric oxygen therapy (HBO) sessions, physical therapy, and massage since the very first day after surgery are advisable.

3.2.11. Therapeutic approach for patients with multiple and multi-level injury to the spine

There are a few combinations of multiple spinal injuries:

1. Complicated fracture of one or more vertebrae and uncomplicated fracture of one or more other vertebrae.

2. Uncomplicated unstable injury to one or more vertebrae and a stable injury to one or more other vertebrae.
3. The following combinations of a multi-level injury to the spine may occur:

1. Complicated injury at one level and uncomplicated injury at the other level (both injuries to the spine are stable);
2. Complicated injury at one level and uncomplicated injury at the other level (both injuries to the spine are unstable);
3. Complicated stable spinal injuries at both levels;
4. Uncomplicated unstable spinal injuries at both levels;
5. Uncomplicated unstable injury at one level and uncomplicated stable injury at the other level.

In determining the order of surgical interventions at different levels, it is advisable to follow the following priorities. The level of complicated injury is subjected to surgical intervention in the first place and the level of unstable uncomplicated injury is operated subsequently. Other conditions being equal, more cranial level should be the first one to be operated.

The following principles are met in the surgical treatment:

1. In the adjacent levels of injury, the surgery is performed by one approach (in the case there are 3 or less unaffected vertebrae between the injured ones).
2. If there are 4 and more unaffected vertebrae between the damaged ones, each injured vertebra is advisable to be accessed through different incisions, avoiding the connection of wounds, which will help preventing abscess of the second wound in the case of abscess of the first wound.
3. In case of complete spinal cord injury at different levels, which is detected clinically or according to computed tomography/MRI data, it is necessary to operate on both levels, to perform complete decompression of the spinal canal and restore cerebral fluid circulation (to perform duraplasty in case of damaged DM) at each level, and to complete the surgery either by transpedicular fixation or by a combination of transpedicular and laminar fixation. Anterior spine fusion following the stabilization is obligatory.

3.2.12. Antibiotic prophylaxis

Prescription of broad-spectrum antibiotics on admission is indicated to patients with an open or penetrating injury to the spine.

In spine and spinal cord surgeries, administration of antibiotics (third-generation cephalosporins) at the very moment of surgery is indicated. Repeated introduction of an antibiotic every 6 hours during surgery is prescribed. Also prescribed is the additional administration of an antibiotic after the blood loss of 1 L.

3.3. Complications, preventive measures, and treatment of patients with acute SCI

Complications arising during treatment of spinal patients worsen the clinical course, increase the length of hospital stay, and occasionally result in fatal outcome. Various types of complications occur in 54—82% of spinal patients. All the complications can be divided into two groups: objective (related to features of SCI) and technical ones (related to surgery, surgical technique, and surgical approach). Knowledge of these complications, preventive care and appropriate treatment (see Table) can reduce their number by 2 or 3 times.

3.4. Outcomes

Functional outcomes in patients with acute SCI are advisable to be assessed on the FIM scale (Appendix 5) (recommended). It is also possible to use the Karnofsky scale (Appendix 6).

In order to predict the outcome of trauma in patients with spinal cord injury and a lack of instrumental signs of injury to bone structures, dynamic MRI of the damaged spinal cord is needed to estimate the extent of spinal cord injury and expected response to treatment (an option).
Complications in patients with SCI: preventive care and management

<table>
<thead>
<tr>
<th>Complication</th>
<th>Therapeutic and preventive measures</th>
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| Urinary tract infections                    | 1. Adequate bladder drainage using one of the following methods:  
   — indwelling urinary catheterization using a silicone Foley catheter, which is less susceptible to encrustation.
   The catheter should be replaced every 7 days, and its adequate functioning should be monitored;  
   — indwelling urinary catheterization using a silver-coated Foley catheter (taking into account the possibility of argyria). The catheter should be replaced every 3 or 4 weeks and its functioning should be monitored. The drainage system should remain closed; an urinal being placed above the urinary bladder is unacceptable;  
   — intermittent catheterization with a sterile Nelaton catheter preferably coated with polyvinylpyrrolidone (a lubricant). Catheterization schedule is worked out individually; the recommended rate is 4—6 times a day (depending on diuresis) to ensure adequate bladder drainage;  
   — cystostomy in case of complications (e.g., acute urethritis, orchiepididymitis, decubitus ulcer of urethra, etc.)
  2. Compliance with all aseptic regulations during urinary catheterization
  3. If an indwelling catheter (preferably a silver-coated one) stayed in the bladder over 7 days, one should begin its “training”: leave the catheter clamped and open it for 20 min at least 5 or 6 times a day. Keep the bladder volume up to 400 mL
  4. The administration of broad-spectrum antibiotics (fluoroquinolones, first- and second-generation cephalosporins, aminoglycosides, and inhibitor-protected penicillins, e.g., Monural) with allowance for the data of urine culture and antibiotic sensitivity test. Systemic antibiotic therapy for asymptomatic catheter-associated bacteriuria is not recommended (grade A recommendation)
  5. Electrostimulation of the bladder
  6. Electrophoresis of the bladder area with proserin
  7. Ensuring adequate diuresis: management of fluid intake and infusion therapy
  8. Acidification of the urine under the tendency towards its alkalization due to administration of methionine or ascorbic acid
  9. Ultrasound of kidneys, bladder, and (in males) prostate in the case of exacerbation of the urinary tract infection |
| Pneumonia                                   | 1. Antibiotic therapy
  2. Active and passive breathing exercises
  3. Chest vibromassage
  4. HBO sessions
  5. Therapeutic bronchoscopy
  6. Physical therapy and massage since the second day after surgery
  7. Early activation of a patient
  8. Inhalation therapy, UHF-therapy, and ultraviolet light therapy applied to the chest; muscle electrostimulation |
| Enteroparesis                               | 1. Early nutrition with products containing crude cellulose and vegetable oils; adequate fluid intake
  2. Early HBO sessions
  3. Pharmacological stimulation of intestinal motility
  4. Cleansing enema no less than once every 3 days |
| Pressure sores                              | 1. The use of anti-decubitus mattresses and pillows
  2. Changing patient’s position in bed every 1.5 hours
  3. Rubbing the area of sacrum, greater trochanters, heels, and scapula with either camphor spirit or a mixture of shampoo and vodka (1:1 ratio)
  4. Early activation
  5. Physical therapy, massage
  6. HBO
  7. Active techniques for decubitus ulcers (necrectomy, displaced or free flap grafting, etc.)
  8. Adequate nutrition management, in particular protein nutrition
  9. Skin care; maintaining moisture balance (by using creams, etc.) |
| Pulmonary embolism and deep venous thrombosis of the lower extremities | 1. Administration of low molecular weight heparins (e.g., Fraxiparine) in patients with severe motor deficits within the first 2 weeks after surgery; in long-stay bedridden patients, the heparin treatment subsequently changed to indirect anticoagulant administration up to 3 months. Control of coagulation is required
  2. The use of tilting beds, prescription of heparin, or a combination of both methods
  3. Low-dose heparin combined with the use of compression stockings or muscle electrostimulation of the lower extremities
  4. Duplex Doppler ultrasound to diagnose deep venous thrombosis (once every 5 days)
  5. The three-month preventive treatment for deep venous thrombosis and pulmonary embolism
  6. Placement of a vena cava filter in patients who can undergo anticoagulation, or in those who cannot tolerate anticoagulation therapy and/or have other contraindications
  7. Early patient’s activation
  8. Physical therapy and massage of limbs from the very first day on admission
  9. Elastic compression of the lower extremities |

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### Complication

<table>
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<tr>
<th>Therapeutic and preventive measures</th>
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<td>Sepsis</td>
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<tr>
<td>1. Prevention of urinary tract infections, pneumonia, pressure sores, and wound abscess</td>
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<td>2. Prevention and treatment for enteroparesis</td>
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<td>3. Monitoring the immunological status of the high-risk group patients (i.e., patients with verified antibodies to hepatitis, HIV, and syphilis; patients with poor health; patients with polytrauma)</td>
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<td>4. HBO</td>
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<tr>
<td>Gastrointestinal bleeding</td>
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<tr>
<td>1. Prescription of H2 antagonists or omeprazole for up to 3 weeks</td>
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<td>2. Prescription of glucocorticosteroids only when it is really necessary</td>
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<td>3. Control over the coagulogram</td>
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<td>4. Nutrition</td>
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<td>5. HBO</td>
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<tr>
<td>Postoperative wound infection</td>
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<tr>
<td>1. Intraoperative administration of either second- or third-generation cephalosporins at the very moment of skin incision and at the end of surgery; the antibiotic therapy should be applied until the sutures are removed. Additional antibiotic administration of 1 g every 6 hours during surgery or per the blood loss of 1 L</td>
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<tr>
<td>2. Accurate layered (5 or 6 rows of sutures) wound closure without tension</td>
</tr>
<tr>
<td>3. Wound draining with active aspiration during 1 or 2 days in case of the transpleural approach or in the presence of a wound cavity that cannot be sutured, or if the lacerated DM cannot be completely sutured or after its suturing</td>
</tr>
<tr>
<td>4. If wound abscess occurs at the site of fixators, perform revision of the wound, sampling for culture and antibiotic sensitivity, necrectomy, and wound drainage. Prescription of broad-spectrum antibiotics; after the results of the culture test — according to the sensitivity. Wound drainage with Lavasept and Dioxydin during 7—14 days. Remove the foreign bodies (metal fixators and other implants) if the conservative treatment during a month was ineffective</td>
</tr>
<tr>
<td>5. In the case of superficial infection, remove sutures, perform sampling for culture test, clean the wound using antiseptics, and keep it open by administration of enzymes and antibacterial ointments</td>
</tr>
<tr>
<td>6. HBO</td>
</tr>
<tr>
<td>Liquorrhea; DM injury</td>
</tr>
<tr>
<td>1. Duraplasty for DM lesions</td>
</tr>
<tr>
<td>2. Accurate suturing of DM via interrupted sutures</td>
</tr>
<tr>
<td>3. After DM is sutured, the Queckenstedt's test must be completed</td>
</tr>
<tr>
<td>4. Wound drainage during 4—9 days</td>
</tr>
<tr>
<td>5. Lumbar drainage for 3 to 5 days or daily lumbar puncture to remove 50—70 mL of cerebrospinal fluid</td>
</tr>
<tr>
<td>6. Application of a hemostatic gauze on DM (or the use of modern fibrin glue compositions such as Tachocomb and Evicel or dural sealant products such as DuraSeal Xact)</td>
</tr>
<tr>
<td>Poor placement of a plate</td>
</tr>
<tr>
<td>1. Knowledge of the placement technique and features of applied plates</td>
</tr>
<tr>
<td>2. Intraoperative control using image intensifier</td>
</tr>
<tr>
<td>3. Reoperation with plate replacement</td>
</tr>
<tr>
<td>Dislocation of screw(s) and a plate</td>
</tr>
<tr>
<td>1. The use of plates and screws with locking mechanisms</td>
</tr>
<tr>
<td>2. Placement of screws under image intensifier control (prevent them from entering the disc)</td>
</tr>
<tr>
<td>3. Check a plate to fit snugly against the vertebral bodies (congruence) to ensure that it does not act like a lever pulling out the screws. <em>The plate should fix vertebrae and a graft, but should not correct and hold the spinal axis!</em></td>
</tr>
<tr>
<td>4. In a long segment fixation (of more than 4 vertebrae), chronic vertebral dislocations, or vertebral dislocations in patients with Bechterew’s disease, anterior spine fixation must be combined with posterior spine fixation</td>
</tr>
<tr>
<td>5. No non-certified or poorly engineered units should be used</td>
</tr>
<tr>
<td>6. Removal of dislocated parts and revision fixation with revision screws with allowance for past mistakes (e.g., while adjusting plates, etc.)</td>
</tr>
<tr>
<td>Screw or plate breakage</td>
</tr>
<tr>
<td>1. Careful selection and designing of a bone graft to ensure full maximal contact with the adjacent vertebrae (a breakage can be caused by graft resorption or the absence of bone block)</td>
</tr>
<tr>
<td>2. The use of polyaxial screws or dynamic plates</td>
</tr>
<tr>
<td>3. Early removal of the hard cervical collar (earlier than 2 months) is unacceptable</td>
</tr>
<tr>
<td>4. No non-certified and poorly engineered units should be used</td>
</tr>
<tr>
<td>5. Broken parts should be removed. Restabilization of the spine is required if a bone block failed to be formed</td>
</tr>
</tbody>
</table>

---

**Table (continued)**
### Table (continued)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Therapeutic and preventive measures</th>
</tr>
</thead>
</table>
| Spinal cord injury                  | 1. Working with adapted instruments and only in the “toward himself” direction  
2. Careful surgery planning, including the preoperative and intraoperative measurements of the length of all grafts according to the individual sizes of patient’s bone structures  
3. When working with bone structures alongside the spinal cord, the hands should not left unsupported: hand rest is always required, and the spinal cord must be covered by an instrument (a special spatula)  
4. In spinal cord injury, begin to administer a high dose of Metypred (according to the scheme) in the very first minutes after injury and to perform HBO sessions immediately after surgery and over the following 10—15 days |
| Nerve root injury, radiculopathy    | 1. Work with neural structures only under oversized visual control  
2. Prescription of NSAIDs, pulsed high-dose dexamethasone therapy for 3 days (40—80 mg per day), and HBO sessions  
3. MRI control to confirm the absence of root compression |
| Carotid artery injury               | 1. Knowledge of the anatomy and careful observance of the surgical approach technique are required  
2. Close the arterial wall defect without assistance. If some doubts appear, cover the defect with a finger to stop bleeding while maintaining the blood flow, apply a vascular clip, and invite the vascular surgeon if the finger pressing failed |
| Superior jugular vein injury        | 1. Knowledge of the anatomy and careful observance of a surgical approach technique are required  
2. Close the venous wall defect without assistance. If some doubts appear, place a vascular clip and invite a vascular surgeon |
| Vertebral artery injury             | 1. Knowledge of the anatomy and careful observance of the surgical approach technique are required  
2. If quick application of the vascular clips above and below the injury site is possible, resect the anterior walls of the transverse processes of one or two vertebrae, separate the artery, and clamp its wall  
3. Plug the injured site of the artery using a fibrin sealant hemostatic. If the medial arterial wall is injured during corporectomy, put a bone graft (accoding to the cavity size) covered with a hemostatic sponge moistened with fibrin adhesive into the cavity of the removed vertebra. Put the sponge on the upper part of the bone graft once again and secure everything with a titanium plate  
4. If bleeding cannot be stopped without assistance, the injured site should be plugged. Then (a) invite a vascular surgeon; (b) identify the site of branching of the vertebral artery (to the left of the aorta, to the right of the thyrocervical trunk) and close it at this site, as close as possible to the entry into the transverse hole of the C6 vertebra. Distally, perform the resection above the injury site of the transverse process and ligate the artery in its own canal |
| Recurrent nerve injury              | 1. Knowledge of anatomical features of the pathway of the nerve, on the left and on the right  
2. Use the left-side approach  
3. Application of Farabeuf hooks or their analogs as retractors (but not the Caspar retractor); esophagus and trachea should not be extended in the medial direction but lifted and be released every time the surgeon does not work in the wound  
4. Coagulation should not be used in the area of surgical approach, the esophagus, and trachea  
5. Prescription of NSAIDs and HBO |
| Temporary dysphonia                 | 1. Reduce the intraoperative traction impact on the surrounding tissues  
2. Prescription of NSAIDs and HBO; vertical position of the patient |
| Esophagus injury, trachea injury    | 1. Knowledge of the anatomy and careful observance of surgical approach technique: the approach to the cervical spine deeper than the platysma is conducted almost blindly; avoid to work anterior to the vertebrae in the pleural cavity  
2. Close the trachea or esophagus walls according to the adopted technique, but better option is to invite a thoracic or general surgeon  
3. Microbial analysis of a wound specimen. Careful debridement of a wound, repeated bathing of a wound with antiseptics  
4. Wound drainage  
5. Prescription of broad-spectrum antibiotics  
6. In plate fixation, make sure that the esophageal wall does not get under the plate  
7. Use licensed implants and adhere to the technology of their placement |

Table is continued on the next page
<table>
<thead>
<tr>
<th>Complication</th>
<th>Therapeutic and preventive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horner’s syndrome</td>
<td>Do not shift within a wound too much lateral, especially when accessing the lower cervical vertebrae</td>
</tr>
<tr>
<td>Thoracic duct injury</td>
<td>1. When accessing the low cervical spine, do not exceed 1—1.2 cm when moving laterally from the center of the vertebra. When accessing the thoracic cage, separate the pleura 2 cm lateral to the heads of ribs and pull it in the anterior direction, carefully skeletonizing vertebrae without cutting the surrounding tissues</td>
</tr>
<tr>
<td></td>
<td>2. Thoracostomy</td>
</tr>
<tr>
<td></td>
<td>3. If the drainage is ineffective and lymphorrhrea is continued, revise the upper thoracic duct up to its entry into the left venous angle (rarely, the duct may end by joining the left internal jugular vein or left subclavian vein) and either close the ruptured site or perform duct plasty together with a vascular surgeon</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1. When accessing the lower cervical or upper thoracic vertebrae, do not shift in the lateral direction</td>
</tr>
<tr>
<td></td>
<td>2. Avoid lung injury</td>
</tr>
<tr>
<td></td>
<td>3. Close carefully the pleural cavity; place the drainage through a counter-aperture incision making a passage under the skin</td>
</tr>
<tr>
<td></td>
<td>4. Thoracostomy</td>
</tr>
<tr>
<td></td>
<td>5. Rapid drain removal (spiratory) from the pleural cavity followed by applying a gauze to the area of removal</td>
</tr>
<tr>
<td></td>
<td>6. X-ray control of the lungs after surgery and in dynamics</td>
</tr>
<tr>
<td>Hematoma at the donor site</td>
<td>1. The use of oscillating saws or bone cutters, which provide hemostasis</td>
</tr>
<tr>
<td></td>
<td>2. Hemostasis of the transplant bed by applying box wax, osteoinductive materials (e.g., Kollapan), or modern hemostatic agents such as Surgiflo, etc.</td>
</tr>
<tr>
<td></td>
<td>3. Careful wound closure with no cavities to be left but capturing the previous layer</td>
</tr>
<tr>
<td>Steady pain in the donor site</td>
<td>1. Compliance with grafting and wound closure techniques to avoid injury to the external cutaneous nerve of thigh</td>
</tr>
<tr>
<td></td>
<td>2. Intraosseous blockades</td>
</tr>
<tr>
<td></td>
<td>3. The use of a bone allograft, bone-substitute materials, and implants</td>
</tr>
<tr>
<td>Suppuration of the donor site</td>
<td>1. The use of oscillating saws or bone cutters, which provide hemostasis</td>
</tr>
<tr>
<td></td>
<td>2. Careful hemostasis of the transplant bed of the removed graft</td>
</tr>
<tr>
<td></td>
<td>3. Careful wound closure with no cavities to be left and with the capture of the previous layer</td>
</tr>
<tr>
<td></td>
<td>4. In the case of wound abscess, perform surgical revision, collect a specimen for culture and antibiotic sensitivity test, and perform necrectomy and drainage. Prescription of broad-spectrum antibiotics; prescription of antibiotics according to sensitivity after obtaining the results of microbial analysis</td>
</tr>
<tr>
<td>Fracture, resorption, or breakage of a bone graft</td>
<td>1. Carefully adjust a graft according to the size of a bone defect and clear it from the connective tissue: the graft should be tightly adjacent to the surrounding vertebrae</td>
</tr>
<tr>
<td></td>
<td>2. Adequate fixation of a graft with a plate selected by size to ensure mild compression of the surrounding vertebrae</td>
</tr>
<tr>
<td></td>
<td>3. The walls of a resected vertebra should be adjacent laterally to the graft; there should be no space between them and the graft</td>
</tr>
<tr>
<td></td>
<td>4. Apply a hard cervical collar after surgery for at least 2 months to prevent redundant mobility and the onset of instability at the surgical level</td>
</tr>
<tr>
<td></td>
<td>5. Reoperation</td>
</tr>
<tr>
<td>Anesthesia, hyperesthesia, chronic pain</td>
<td>1. Compliance with grafting and wound closure techniques to avoid injury to the external cutaneous nerve of thigh</td>
</tr>
<tr>
<td>along the lateral surface of the thigh</td>
<td>2. Anesthesia, HBO, massage, and physical therapy</td>
</tr>
<tr>
<td>Postoperative wound hematoma</td>
<td>1. Careful observance of surgical technique</td>
</tr>
<tr>
<td></td>
<td>2. Adequate hemostasis</td>
</tr>
<tr>
<td></td>
<td>3. Wound drainage (with intact DM — active aspiration)</td>
</tr>
<tr>
<td></td>
<td>4. Control of patient’s coagulation; correction in case of disorders</td>
</tr>
<tr>
<td></td>
<td>5. Apply cold to the area of operative wound immediately after surgery and during 6—8 hours postoperatively in sessions of 15 to 20 min with a 15-minute break</td>
</tr>
<tr>
<td></td>
<td>6. The use of newer hemostatic agents (Surgicel, Surgiflo, etc.)</td>
</tr>
<tr>
<td></td>
<td>7. If hemorrhage continues, perform revision of a wound (hemostasis)</td>
</tr>
</tbody>
</table>
APPENDICES

Appendix 5

The functional independence measure (FIM) (according to C. Grangery et al., 1979 and L. Cook et al., 1994).

A seven point ordinal scale for rating tasks:

7 — Complete independence to perform relevant task (patient can perform the task without assistance, in the ordinary way, spending reasonable time)
6 — Modified independence (patient can perform the task without assistance but slower than usual, or needs supervision)
5 — Supervision or Setup (patient requires supervision or assistance while putting on prosthesis and/or orthosis)
4 — Minimal assistance (patient requires assistance but can perform 75% or more of the task)
3 — Moderate assistance (patient can perform 50% to 75% of the task without assistance)
2 — Maximal assistance (patient can perform 25% to 50% of the task without assistance)
1 — Total assistance (patient can perform less than 25% of the task without assistance)

Table to Appendix 5

<table>
<thead>
<tr>
<th>Reply form</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self care</strong></td>
<td></td>
</tr>
<tr>
<td>1. Eating (the use of utensils, bringing food to the mouth, chewing and swallowing)</td>
<td></td>
</tr>
<tr>
<td>2. Grooming (brushing teeth, hair grooming, washing face and hands, shaving or applying make-up)</td>
<td></td>
</tr>
<tr>
<td>3. Bathing/shower (washing and drying the body except the back)</td>
<td></td>
</tr>
<tr>
<td>4. Dressing the upper body (above the waist, including applying prostheses/orthoses)</td>
<td></td>
</tr>
<tr>
<td>5. Dressing the lower body (down the waist, including applying prostheses/orthoses)</td>
<td></td>
</tr>
<tr>
<td>6. Toileting (cleanse himself/herself after visiting the toilet, the use of sickness bags)</td>
<td></td>
</tr>
<tr>
<td><strong>Control of pelvic organ function</strong></td>
<td></td>
</tr>
<tr>
<td>7. Bladder (control of urinary bladder and, if necessary, the use of equipment for urination, e.g., catheters, etc.)</td>
<td></td>
</tr>
<tr>
<td>8. Bowel (control of bowel movements and, if necessary, the use of a special equipment, e.g., enemas, colostomy bags, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>Transfer</strong></td>
<td></td>
</tr>
<tr>
<td>9. Bed, chair, and wheelchair (transferring to and from a bed, chair, and wheelchair)</td>
<td></td>
</tr>
<tr>
<td>10. Toilet (the ability to use the toilet, i.e. getting on and off a toilet)</td>
<td></td>
</tr>
<tr>
<td>11. Tub and shower (the ability to use a tub/shower)</td>
<td></td>
</tr>
<tr>
<td><strong>Locomotion</strong></td>
<td></td>
</tr>
<tr>
<td>12. Walking (locomotion) using a wheelchair (score of 7 corresponds to the ability to walk without assistance 50 m or greater; score of 1 indicates the inability to walk a distance over 17 m)</td>
<td></td>
</tr>
<tr>
<td>13. Walking up the stairs (score of 7 corresponds to the ability to walk up 12 to 14 stairs without assistance; score of 1 indicates the inability to go up more than 4 stairs)</td>
<td></td>
</tr>
<tr>
<td><strong>Motor function (total score):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Communication</strong></td>
<td></td>
</tr>
<tr>
<td>14. Cognitive comprehension (understanding of auditory and/or visual information)</td>
<td></td>
</tr>
<tr>
<td>15. Expression of his/her own wishes and thoughts (verbally or in written form)</td>
<td></td>
</tr>
<tr>
<td><strong>Social interaction</strong></td>
<td></td>
</tr>
<tr>
<td>16. Social integration (interaction with family members, medical staff, and other environment)</td>
<td></td>
</tr>
<tr>
<td>17. Problem solving (the ability to make decisions regarding the financial, social, and personal affairs)</td>
<td></td>
</tr>
<tr>
<td>18. Memory (the ability to memorize and retrieve visual and verbal information, the ability to learn and to recognize people)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognition (total score):</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 6

### Table to Appendix 6

**THE KARNOFSKY SCALE**

Medical assessment of the patient’s performance status (is completed by the doctor in charge once every two weeks)

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparently healthy; no complaints; no evidence of disease</td>
<td>Able to carry on normal daily activity; no special care is needed</td>
<td>100</td>
</tr>
<tr>
<td>Able to carry on normal daily activity; minor signs or symptoms of disease</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Normal daily activity with effort; some signs or symptoms of disease</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Unable to work, able to live at home and care for most personal needs; a varying degree of assistance is needed</td>
<td>Able to care for self; unable to carry on normal daily activity or to do active work</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Able to care for most of his/her own needs but occasionally requires assistance</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Able to care for some of his/her own needs. Requires considerable assistance and frequent medical care</td>
<td>50</td>
</tr>
<tr>
<td>Unable to care for self, requires hospital care; disease may be progressing rapidly</td>
<td>Disabled, requires special care and medical assistance</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Severely disabled, hospitalization is indicated although death is not imminent</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Very sick: hospitalization and active supportive treatment are a must</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Moribund: fatal processes progressing rapidly</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>
REFERENCES

35.Дени Ф. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine 1983; 8: 817—831.
Current State of Surgical Treatment of Insular Gliomas

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¹Burdenko Neurosurgical Institute, Moscow, Russia; ²Moscow Regional Research Clinical Institute, Moscow, Russia

Intracerebral tumors of the insular lobe are quite frequent. However, management of these patients remains challenging and controversial. This is mainly due to location of tumors in the area that is close to vital anatomical structures (the M1—M2 segment of the middle cerebral artery, lenticulostriate arteries, basal ganglia, and the internal capsule). For this reason, the incidence of postoperative complications in these patients is still high. The purpose of this study was to analyze the literature related to the issues of clinical presentation, diagnosis, and aspects of surgical treatment of intracerebral tumors of the insular lobe.

**Keywords:** insular lobe, intracerebral glial tumors.

The Island of Reil, or insular lobe, named after the famous German anatomist, physiologist, and psychiatrist Johann Christian Reil (1759—1813), who wrote a comprehensive monograph [1] about this “hidden portion of the cerebral cortex” in 1809 and entitled it “die Insel” [2], i.e. islet. It is also believed that the first relatively detailed illustrations of the insula were published in 1611 in the book of Caspar Bartholin (1585—1629) “Anatomicae Institutiones Corporis Humani”. Schematic representation of the insula can be found in the work of the prominent anatomist Andreas Vesalius (1514—1564) “On the structure of the human body in seven books” (De Humani Corporis Fabrica Libri Septem, 1543). English surgeon and anatomist Alexander Monro depicted three short gyri of the insula in the sagittal plane (after removing the anterior portion of the frontal lobe) in his book “Observations on the structure and functions of the nervous system” (1783). However, he did not give them anatomical names [3].

After publication of the works of I.H. Reil [1, 2], little attention was paid to the insular cortex. Only since 1860, the interest to the insula was renewed due to the rapid development of neurological doctrine of localization of functions in the brain. The relation between the insular lobe and surrounding structures and its role in the language function were the main issues of interest to scientists of the time. Renowned French surgeon, anatomist, and anthropologist Paul Pierre Broca, 1824—1880 identified the location of the motor speech center in the left frontal operculum and thus denied the role of insula based on the findings of the autopsy of patients with and without aphasia. The Austrian physician and anatomist Oscar Eberstaller gave the earliest modern and the most complete morphological characteristics of insula. His description of the insula lobe and terminology [4] formed the basis for subsequent studies. Another fundamental work was the book of the Austrian psychiatrist and neurologist Constantin von Economo (1876—1931) “Anatomy of the brain” [5], which described in detail sulci and gyri of the insular lobe of the brain and determined the exact anatomical nomenclature, which we use at present.

It was not immediately that the insula gained recognition as a true cerebral lobe. At the I International Congress of Anatomists held in 1888 in Basel, the following four cerebral lobes were recognized: frontal, parietal, occipital, and temporal, while the insula was regarded as a separate entity, rather than a lobe. It was only after the X International Congress of Anatomists (Tokyo, 1975) that the insula has been identified as a fifth cerebral lobe.

**The anatomy of the insular cortex**

Insula cannot be considered as a rudimentary portion of the brain, as the complexity of organization of this lobe gradually increases from primates to humans. For example, studies showed that the insula has either no gyri or just a single orbitoinsular sulcus in macaques (depending on species) [6, 7]. The human insula has 5—7 sulci and gyri and its volume is much greater compared to that in monkeys. At the same time, the insula is most developed (for unknown reasons) in cetaceans, up to 20 sulci. The insula is the only cerebral lobe that in not exposed on the surface. It is covered from top to bottom with portions of the frontal, parietal and temporal lobes, which form three opercula, respectively, whose adjoining surfaces in turn form a deep portion of Sylvian fissure. When removing the opercula, the insula will appear as an inverted pyramid with its base facing the frontal lobe. The central sulcus of the insula divides its surface into two parts: the larger (anterior) and smaller (posterior). The anterior part consists of three separate short gyri (anterior, middle, and posterior), as well as an accessory and transverse gyri, which are not always present. The posterior part of the lobe consists of two long gyri, the anterior and posterior ones. All gyri converge to the top of the insula, which is the most projecting part of the insular lobe. Limen insulae is another distinguished part of the insula. It is a slightly elevated arched edge, located at the junction of the sphenoidal and opercular segments of the Sylvian fissure [8]. The uncinate fascicle is located under the grey matter covering the limen insulae. The anterior perforate substance is located just below and medial to the limen insulae. According to different authors [9, 10], the average distance between the entrance of the most lateral lenticulostriate artery into the anterior perforate substance and the medial edge of the limen insulae is 15 to 20 mm. Capsula extrema, claustrum, capsula externa, putamen, globus pallidus, and capsula interna are located under the central part of the insula in the lateral-medial direction (see Figure).

The perimeter of the insula is bounded by superior, anterior, and inferior peri-insular gyri, which separate the insula from the surrounding opercula. The M2 segment of the middle cerebral artery lies on the lateral surface of the lobe.
Perforating vessels feeding the insula run from the M2 segment. According to the study of U. Türe et al. [12], about 85—90% of insular arteries are short and supply only to the insular cortex and capsula extrema, 10% of arteries are average and reach the claustrum and capsula externa, and only 3—5% of arteries are long, supplying the radiant crown. Thus, injury of the latter during the resection of insular tumors can lead to hemiparesis.

The M1 segment of the middle cerebral artery is located under the antero-inferior part of the insula. Lateral lenticulostrate arteries supplying the basal ganglia and capsula interna run from the M1 segment.

**The function of the insular lobe**

The insula belongs to the paralimbic system, the part of the central nervous system serving as a link between the limbic system (allocortex) and the cerebral hemispheres (neocortex). It is represented by mesocortex, i.e. it has 3 to 5 layers of neurons.

The function of the insula has long been a subject of heated debate among researchers. Even today there is no consensus on this issue. For example, clinical cases of ischemic infarctions localized only in the insula manifest as a variety of symptoms depending on the location and distribution of the pathological process. C. Cereda et al. [13] distinguish the following 5 main symptom complexes of the insular cortex injury: somatosensory deficit (infarction in the posterior lobe of the right/left insula), ageusia (posterior lobe of the left insula), vestibular syndrome (posterior lobe of the left/right insula), cardiovascular disorders (infarction in the posterior lobe of the right insula), and neuropsychological symptoms (ischemic injury of the posterior parts of the left/right insula).

Interesting results were obtained by A. Afif et al. [14] in a study of 25 patients with pharmacoresistant epilepsy, who were stereotactically implanted with electrodes into the insular lobe. Indications for their implantation into the insula included both clinical manifestations of seizures (taste hallucinations, discomfort in the throat, paresthesia and tonic-clonic contractions of facial muscles, and hypersalivation) and videoencephalogram data.

The following responses were obtained as a result of direct stimulation: speech disorder (inability to speak or decreased voice intensity) — 8, pain (in the craniofacial area or stabbing pain in the contralateral side of the body) — 8, somatosensory symptoms (paresthesia and heat sensation) — 11, motor responses — 11, oropharyngeal symptoms (throat tightness and suffocation) — 8, auditory phenomena (ringing and buzzing) — 3, neurovegetative symptoms (throat flushing, dizziness, nausea, discomfort in the epigastric region, burning sensation) — 20.

Thus, the insula is involved in processing of sensory impulses (smell and taste), control of autonomic functions (the sympathetic control of the cardiovascular system), emotional and behavioral responses, as well as voluntary swallowing and speech modulation process. The insula is probably a part of the neuronal system connecting supramarginal gyrus with Broca’s area, and can participate (along with the premotor cortex) in phonetic planning of speech [15-17].

**Classification of insular tumors**

In 1992, M. Yaşargil et al. [18] published preliminary results of treatment of patients with tumors of the limbic and paralimbic systems. In this work, which later became a classic
one, the authors identified the following three main types of tumors affecting the insular lobe: 3A type tumor is located within the insula, 3B type tumor is a space-occupying mass that spreads to the adjacent opercula, 5 type tumor expands beyond the frontal and temporal opercula to the orbitofrontal or temporopolar areas. (Other types of tumors according to this classification are as follows: 1 — space-occupying mass in mediobasal regions of the temporal lobe, 2 — cingulated gyrus tumors, 4 — lesions of fornix and mammillary bodies).

For a long time, it was the only classification. The new classification was proposed only in 2010 by N. Sanai et al. [19]. The authors partitioned the insula with two perpendicular planes passing through the foramen of Monro and Sylvian fissure. As a result, the insula is divided into four zones as follows: I — the anterosuperior zone, II — posterosuperior zone, III — posteroinferior zone, and IV — anteroinferior zone. If the tumor expands beyond one zone, it is designated as the sum of zones, in which it is locates. In cases where the mass lesion occupies all zones and goes beyond them, it is referred to as giant one.

Features of insular gliomas

According to recent epidemiologic data, insular gliomas account for 10 and 25% of the number of all high-grade and low-grade brain gliomas, respectively [20] and exhibit properties that make them distinct from tumors located in other parts of the brain.

According to epidemiological studies [18], there is a clear trend to low-grade tumor growth in the insula (Table 1).

Less aggressive tumor growth is observed in patients with low-grade tumor in the insula compared to patients with the same pathology at other sites. Some researchers [19] highlight cytoarchitectonic features of this area (mesocortex) and functional features of this lobe, but the exact cause of this phenomenon has not yet been fully understood.

Surgical treatment of insular tumors

There is a high risk of augmentation of neurological deficits after resection of insular tumors since the insula is located close to the most important vascular and nerve structures. Severe hemiparesis and significant speech disorders can occur in the postoperative period, if the tumor is located in the dominant hemisphere for speech. For this reason, some authors [25—27] believe that these tumors are inoperable. Stereotactic biopsy with verification of histological diagnosis followed by radiotherapy and/or chemotherapy is considered to be the method of choice in this case [28, 29]. Although there is much debate regarding the need for radical resection of brain gliomas, some researchers [26, 30—32] still believe that it is important to improve the life prognosis in patients.

M. Yaşargil et al. [18] were among the first who substantiated the possibility to remove these tumors with good neurologic outcomes after surgeries interventions in many patients. Their study involved 57 patients with insular and insulo-opercular tumors and 23 patients with fronto-insulo-temporal tumors. Despite the fact that 67% of tumors were greater than 5 cm in diameter and 53% of tumors were located in the left hemisphere, bulk resection was apparently achieved in most cases. However, they did not report the extent of resection in each case. In most patients, tumors were benign and did not cause significant neurologic deficits. After surgery, moderate neurologic disorders in the form of hemiparesis, which required rehabilitation, developed in 8 (14%) patients in group 1 and in 1 (4%) patient in group 2. The authors did not mention speech disturbances in their report. After the publication of M. Yaşargil, several works were published, in which a smaller number of patients was analyzed. Thus, V. Vanaclocha et al. [30] reported on their experience in surgical treatment of 23 patients with insular tumors, which were located in the left hemisphere in 70% of cases. According to MRI, total resection was achieved in 20 of 23 cases. Postoperative deficit in the form of hemiparesis and dysphasia developed in 6 patients. J. Zentner et al. [31] reported on a detailed analysis of 30 cases of insular tumors. In general, taking into account pre- and post-operative MRI, total resection was achieved in 17% of cases, subtotal resection was achieved in 70% of cases, and partial resection was achieved in 13% of cases. In this study, hemiparesis occurred in 4 patients, and aphasia occurred in 3 patients. As a result, the authors state that postoperative period was quite difficult in 63% of patients and that surgical interventions in the insular region is associated with substantial risk (Table 2).

There are several basic surgical approaches to insular tumors: 1) transsylvian 2) transcortical (transfrontal or transtemporal) and 3) combined (transcortical + transsylvian). Only transsylvian approach was used in the innovative work of M. Yaşargil et al. [18]. However, there is currently no common opinion in the world literature on the most optimal approach in terms of safety and the possibility of maximum visibility of tumor margins for its maximal resection. Some authors [30, 34—36] used transsylvian approach only for isolated insular tumors. In cases when tumor spread to the frontal and temporal areas, they began resection with transcortical approach and only then used transsylvian approach. Other authors [18, 23] preferred to use only transsylvian approach even for fronto-insulo-temporal tumors. Complexity of this approach is associated with the possibility of injury to veins and arteries of the Sylvian fissure, which leads to ischemia and, as a consequence, to postoperative deterioration of neurologic functions. Traction of the opercular area during this approach can also lead to postoperative deterioration [24].

Table 1. The ratio of high-grade (Grade III—IV) and low-grade (Grade I—II) insular gliomas, the results of histological examination of the preceding series

<table>
<thead>
<tr>
<th>Author of the publication, year</th>
<th>Number of patients, n</th>
<th>Insular glioma grade in patients, % of n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>M. Yaşargil et al., 1992 [18]</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>J. Zentner et al., 1996 [31]</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>V. Vanaclocha et al., 1997 [30]</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>F. Lang et al., 2001 [35]</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>H. Duffau, 2009 [27]</td>
<td>51</td>
<td>0</td>
</tr>
</tbody>
</table>
If the tumor is located in the dominant hemisphere (Broca's and Wernicke's area), than motor and language zones can be damaged when using transcortical approach. H. Duffau et al. [26, 27] used electrophysiological stimulation of the cortex and pathways in all patients (51) during surgery to avoid complications when using transcortical approach. In 16 of these cases, awake craniotomy was performed. Despite the deterioration in 30 (59%) cases immediately after surgery, only two patients retained neurological deficit in future. Postoperative MRI showed that 16% of resections were total, 61% of resections were subtotal, and 23% of resections were partial. Lang et al. [35] used only transsylvian approach when operating patients with insular tumors (22 patients). They used frameless navigation to optimize surgical approach. In all cases, electrophysiological stimulation was performed. Ultrasound navigation allowed a certain degree of control over the extent of tumor resection. As a result, total resection was achieved in 10 patients, and in the remaining 12 patients, resection was in equal proportions subtotal (6) and partial (6). In the late postoperative period, neurological deficit remained only in 2 patients. The authors believe that the main reason for this phenomenon was the damage to lenticulostriate arteries only during the operation. F. Lang et al. [35] thoroughly analyzed mutual arrangement of these arteries and tumors according to preoperative MRI (standard mode) and properly planned the extent of the surgery in order to reduce the risk of crossing these arteries during tumor resection. In previous studies, H. Duffau [27] used preoperative CT angiography for this purpose. In recent publication [36], it was suggested to use 3D TOF MRI, which, according to the authors, most clearly reflects topographic and anatomic relationship between lenticulostriate arteries and tumor. Only two recent large-scale studies (M. Simon et al. [37], N. Sanai et al. [19]) provided a detailed analysis of survival rate of patients with insular tumors depending on their histology and extent of resection. The study of M. Simon et al. [37] included 94 patients, 36% of them had benign gliomas and 64% had malignant gliomas. As a result, the 5-year overall and relapse-free survival was 68 and 58% for Grade II gliomas, 83 and 80% for anaplastic oligodendrogliomas, and 61 and 51% for anaplastic astrocytomas, respectively. Recently, N. Sanai et al. [19] analyzed the outcomes of treatment of 104 patients, of whom 60% had benign gliomas and 40% had malignant ones. As a result, the 5-year overall survival of the patients operated for Grade II gliomas was 100% in the case of resection rate higher than 90% and close to 84% in the case of resection rate lower than 90%. In the same context, the 2-year overall survival in patients operated for malignant gliomas was 91% in the case of resection rate higher than 90% and close to 75% in the case of resection rate lower than 90%. As a result, the authors concluded that the extent of resection significantly affects the overall and disease-free survival.

**Conclusion**

Despite the complexity of the anatomy of the insular region of the brain, recent studies have shown that aggressive resection of insular gliomas is feasible and frequency of postoperative neurological deficits is acceptable.

**REFERENCES**

Insular gliomas are quite common in clinical practice, but the complexity of anatomical and topographical relations between insular structures affected by infiltrative tumors, surrounding functionally important structures, which are often deeply buried, and major trunks of MCA system cause objective difficulties in surgical treatment of these structures. Development of microsurgical complex allows overcoming these problems in many respects. However, it requires precise targeted assessment of various aspects of this microneurosurgical oncologic problem to reduce the severity of neurological adverse events in the early and late postoperative periods. All these facts necessitate the search for ways both to improve the early diagnosis of insular tumors and to develop algorithm for microneurosurgical methods of resection of these complex tumors.

The authors presented an in-depth review of the literature on all components of this complex problem, including anatomical and topographic features of this cerebral structure, its functional significance, classification of intra-insular tumors, main clinical manifestations, surgical treatment, and its main results. The anatomical picture and the results of a number of studies, which clearly illustrate the main points of the article, are provided.

This work is undoubtedly interesting and instructive and contains practically important information. It can become the subdiscipline of microneurosurgery.

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